Semimicro Qualitative Organic Analysis

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Preface

For the past several years the authors of this book have become increasingly interested in the possibilities of improving and greatly expanding the scope of qualitative organic analysis by the application of semimicro techniques. After long and careful laboratory experimentation and testing with all types of students, they are now thoroughly convinced of the practicability and decided advantages inherent in the use of these newer methods.

Specifically, the use of small quantities (1) reduces materially the time required for most operations. (For the student these savings in time make possible more varied experience in the same laboratory period.) (2) It cuts the cost of chemicals to 20% or less than that required for the old methods. (For institutions and students with limited budgets, this saving multiplies the number of students who can take the course.) (3) It permits the analysis of samples too small for proper identification by old methods. (This possibility is of special significance to industrial chemists and laboratory workers.) (4) It reduces the seriousness of possible accidents. (5) It instills in the student superior habits of care, cleanliness, and manipulative skill. (6) It allows for great flexibility in adapting the work to the interests and abilities of individual students.

In organizing and writing this book, the authors have kept in mind the needs of three major types of users: industrial chemists and laboratory workers in chemically related fields (for example, hospital technicians, toxicologists, and Boards of Health workers); students enrolled in regular college courses in qualitative organic analysis; and students in first-year organic chemistry.

The idea of using this book for laboratory work with students in their first year of organic chemistry is probably so radical at the present time as to deserve special comment. Some of the reasons justifying this departure are:

1. Students find the work more interesting than with the usual laboratory procedures and therefore apply themselves better.

2. The work involves a greater use of chemical theory than does the usual type of laboratory work.

3. The work of each student can be more readily and objectively evaluated because individual "unknowns" are given.

The authors sincerely believe that this combination text, manual, and reference book makes it practicable for the first time to include qualitative organic analysis as an important part of the laboratory work of first-year organic chemistry.

This book contains many features that can be properly evaluated and appreciated only by a careful study of the entire book. However, the detailed descriptions in Chapters 9–13 of the methods used for the preparation of derivatives deserve special mention. These specific directions for procedures have not been merely compiled from the literature but rest on actual labora-

tory experimentation. Their value lies in the fact that they meet the need in semimicro work to insure: (a) completion of the reaction, (b) a minimum number of crystallizations to obtain a pure product, (c) exact quantities of solvent and conditions of crystallization, and (d) sufficient yield of the product for several melting-point determinations. Where a method applicable to one member of a particular group requires alteration for other members of the same group, the text describes the preparation of the same type of derivative for both open-chain and cyclic members of the group, and provides explanatory notes following the preparation of typical derivatives.

Other features worthy of particular attention are as follows:

1. The tables of organic compounds and their derivatives, for which a separate index is provided. In the selection of the compounds every effort was made to include those organic compounds that are commonly met in industrial and organic laboratories. In addition, Table 42 lists about 250 miscellaneous compounds, among which are the common drugs and most important vitamins and hormones. Like the descriptions of methods for the preparation of derivatives, these tables are the result of an exhaustive study of the literature.

2. A system making use of both solubility data and elemental analysis for the tentative classification of unknowns. This plan materially shortens the average time needed in final identification.

3. Detailed illustrations and complete instructions for the preparation of all apparatus and equipment called for by analyses where such apparatus either is not on the market or is not readily available.

Although this work is the product of the joint effort of both authors, the first co-author has assumed the primary responsibility for Chapters 1, 2, 3, 9, 10, 11, 12, and 13, and the tables of derivatives; the second co-author, for Chapters 4, 5, 6, 7, 8, and 14. Dr. Arthur L. LeRosen of Louisiana State University has prepared Chapter 15.

The authors wish to express their sincere appreciation to all those who have assisted in any way with this book. They would like especially to acknowledge their indebtedness to Dr. George H. Coleman, Dean of the Institute of Textile Technology; to the staff of the John Crerar Library of Chicago, particularly Mr. H. Einer Mose, Assistant Chief Librarian; to Dr. Louis Sattler and Dr. David Davidson of Brooklyn College, Dr. Ben Sher of the Chicago Tuberculosis Institute, Mr. Michael Savoy of the Pure Oil Company, Dr. Otis C. Dermer of Oklahoma Agricultural and Mechanical College, and Mr. Denver Cummings of Chicago; and to the many students of both authors who have served so faithfully and well as assistants in testing the adaptation of various general methods for the identification of classes and for the preparation of derivatives to specific preparations in which semimicro techniques are used.

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Semimicro Qualitative Organic Analysis

CHAPTER I

Introduction

IN CHEMICAL work the need often arises for the identification of an organic substance. The unknown compound in question may have been obtained through a chemical reaction, or isolated either from a commercial product or from a mixture derived from natural sources. The usual procedure followed in such identification is to determine whether the compound in question bears *complete similarity* in physical and chemical properties to one of the large number of organic substances described in the chemical literature. In order to determine whether such similarity exists, it is necessary to follow a systematic procedure whereby the unknown compound, by step-wise tests, is assigned to a large class whose members it resembles in one or more physical or chemical properties and to which it therefore bears a *partial similarity*.

Most schemes of qualitative organic analysis begin with the classification of organic substances on the basis of a common property, such as solubility in a particular solvent, or the elements present. The unknown compound is subjected to a number of tests wherein very small samples are made to undergo physical or chemical changes. From the results of these tests inferences are drawn, and the unknown is restricted to fewer and fewer subdivisions of a particular class until it becomes possible, by using all the data obtained, to find a known compound in the literature that shows *complete similarity* and therefore is *identical* with the unknown compound under investigation.

Steps in identification of organic compounds. The scope of the present work is to aid in the development of mental and manual skills for identifying the more common organic compounds systematically in semimicro quantities. The method used involves the following four major steps:

1. *Purification.* The unknown substance is purified, unless it is already known that the compound is pure. The purification involves crystallization or distillation, and therefore the determination of at least one physical constant.

2. *Classification.* The unknown substance is subjected to gross examination and analysis for the elements present. This is followed by solubility tests in a few solvents and functional-class tests, which usually

involve chemical reactions with a number of reagents. On the basis of the elements present and solubility tests, the unknown is assigned to a large *Solubility Division;* by means of specific tests for functional groups the unknown is assigned more particularly to one of the classes of compounds that belong to this large Solubility Division.

3. *Coordination.* All the data, including physical constants, must be carefully coordinated. The literature has to be consulted and a list of compounds prepared; the compound that best fits the data is then selected as the probable one.

4. *Derivatization*[1] *and final proof.* By means of chemical reactions one or more suitable derivatives of the unknown are prepared. If the derivative prepared melts within 1°–2° of the melting point recorded in the literature for the same derivative of the probable compound selected, the identification is regarded as tentative. Finally, if a mixture consisting of the derivative prepared from the unknown and the same derivative prepared from a pure sample of the compound tentatively identified as the unknown, melts without showing a variation of more than 1° from the melting point of either component alone, the proof is considered conclusive. If the unknown is a solid, a mixture of the unknown itself and the tentative compound may be used for determination of the mixed melting point.

To illustrate the steps used in the identification, let it be assumed that the unknown is a liquid. On distillation, 90 per cent boils at 116–118°; analysis of a sample from this fraction for elements shows the absence of nitrogen, halogens, and sulfur. The substance is found to be soluble in water and ether, and therefore is classified (page 109) in *Solubility Division E*, which includes carboxylic acids, alcohols, carbonyl compounds, anhydrides, esters, ethers, and some phenols. Since the aqueous solution of the unknown is neutral, all acidic substances are excluded. Tests of the unknown with a mixture of potassium alkoxide and carbon disulfide (xanthate test, page 125) indicate the presence of an alcohol group, and hence the unknown is restricted to the class of alcohols. Reference to the table on page 370, which lists the alcohols with their boiling points, indicates that, since the unknown has a boiling point of 116–118°, it is probably *n*-butyl alcohol (b.p. 117.7°). One of the recommended de-

[1] Since the noun is *derivative,* this term should be either *derivativization* or *derivativation.* However, since the word derivatization has acquired wide usage and has come to have a technical meaning, the authors feel that it should be retained. Dr. Norris Rakestraw, editor of the Journal of Chemical Education, has expressed somewhat the same opinion. He states: "I am content to use the word as it is, even though it has such doubtful parentage. The only other possibility would be to use *derivation,* but this does not seem to imply the preparation of derivatives."

rivatives for alcohols is the 3,5-dinitrobenzoyl ester, prepared by the reaction of the alcohol with 3,5-dinitrobenzoyl chloride. When the 3,5-dinitrobenzoyl ester of the unknown is prepared, it shows a melting point of 63° after one crystallization; the melting point of the 3,5-dinitrobenzoate of butyl alcohol is given in the literature as 64°. The 3,5-dinitrobenzoate prepared from a known sample of *n*-butyl alcohol is found to melt at 63°, and a mixture of the two dinitrobenzoates (from unknown and known) shows no alteration in the melting point. Another derivative is prepared by the reaction of a sample of the unknown with α-naphthyl isocyanate; the resulting α-naphthylurethan (α-naphthylcarbamate) melts at 71°, which is the melting point listed in Table 5 for the α-naphthylurethan of *n*-butyl alcohol. Therefore the unknown is definitely identified as *n*-butyl alcohol.

Identification of new compounds. In research a compound is often obtained that is new and therefore not previously described in the literature. Since the task of completely characterizing such a compound is rather involved, it is beyond the scope of the present work. The steps, briefly summarized, are: (a) qualitative and quantitative determination of the elements present in the compound; (b) determination of the molecular weight that leads to the derivation of the number of each kind of atoms in the molecule; (c) a thorough study of the reactions of the compound, which permits the formulation of a hypothesis as to the arrangement of the atoms within the molecule of the compound (that is, the *structure* of the compound); and (d) tentative proof of the hypothesis as to the structure of the compound by its transformation into one or more substances of known structure or by its synthesis from other known compounds.

Semimicro techniques. Although there is as yet no general agreement as to the demarcation lines between *macro*, *semimicro*, and *micro* quantities, the authors designate as *microquantities* those involving the use of up to a few milligrams; as *semimicroquantities* those involving the use of up to several hundred milligrams; and as *macroquantities* those involving the use of several grams. Most of the solubility and functional-group tests may be performed by using 50–100 mg of the substance. With a little care it is possible for beginners to perform most tests with quantities as small as 5–10 mg. However, in the final step of identification, beginners starting with only a few milligrams of the unknown find it very difficult to prepare and recrystallize a derivative and still have a sufficient amount for the determination of melting points. For this reason, most of the procedures for the preparation of derivatives have been de-

veloped for the use of 100–200 mg of substance. Once experience is acquired, however, it is possible, without much special equipment, to complete the identification of an unknown compound starting with 5–10 mg of substance. The procedures for the identification of *microgram* quantities will be treated in a later work.

The use of semimicro techniques in the identification of organic compounds, both in industrial and college laboratories, offers a number of advantages, some of which are enumerated in the Preface, but the most important of which is economy in time and equipment.

Method of using this text. How this book will be used will vary with the stage of advancement of the reader and with his purpose in consulting it. Experience has clearly shown that it may be successfully used both by those who are beginning the study of organic chemistry and those who already have advanced knowledge and experience in the field. Some suggestions are offered here as to how the book may be utilized by three different types of readers.

Workers in industry. The chief interest for chemists in industrial and research laboratories will probably be the methods and tests used in the classification of organic compounds and the semimicro techniques used in the preparation of derivatives. If the reader is not familiar with semimicro laboratory procedures, a reading of Chapters 2 and 8 is suggested before any work is undertaken; otherwise the chemist may select from Chapters 4, 5, 6, and 9–13 those methods that apply to the problem at hand. For those who wish to work through the book systematically in order to review and extend their knowledge of organic chemistry, the suggestions given below for advanced students are recommended.

Beginners in organic chemistry. While the facts and theories concerning the various classes of organic compounds are being studied, known members of these classes may be used to perform those tests pertinent to the class being studied. Experience may also be gained in making *preparations* and in typical organic reactions by preparing *derivatives* of these known compounds by several methods. To illustrate, let it be assumed that alcohols are being studied in the lecture course. Three representative alcohols may be selected for laboratory investigation. Their properties may be studied by the general tests for hydroxy compounds (Test 5.6, page 116) and by the specific alcohol tests (Test 6.6, page 125). Further experience with alcohols may be gained by preparing derivatives for selected alcohols (Experiment numbers 10.1–10.7, pages 221–225), purifying them, and then determining their melting points. A comparison may then be made between the data from the experiments and those data given in the tables for the alcohols (page 370).

If an ***unknown*** compound is secured and identified as soon as the preliminary work has been completed with ***knowns*** of any one class, the work will generally prove more interesting and the preliminary work will be done with more care and attention to detail.

Periodically the student may be given an unknown that may belong to any chemical class studied up to that time. The identification of such a compound involves the identification of the chemical class to which the compound belongs before the actual member of the class can be identified. Gross examination (page 85), determination of the elements present (page 88), and solubility data (page 107) yield the facts on which deductions as to the probable chemical class are based. Functional-group tests may then be made for all probable compounds until the proper class is identified. Such work is mentally stimulating and helps in the correlation of facts about the various chemical classes.

Advanced students. Those students who have had one or more courses in organic chemistry may follow the methods of this text systematically. Either one of two courses may be pursued. One course is systematically to study the theory involved and acquire experience in all the methods suggested in the text before undertaking the identification of general unknowns. The other procedure is to start the identification of unknowns early in the course and to study the theory and perform the experiments that seem necessary for each unknown as the need arises. The first method affords a more complete knowledge of the whole subject; the second sustains interest better but generally fails to include many of the functional tests and methods of making derivatives.

A considerable portion of the time spent in identifying unknowns should be devoted to mixtures. Numerous problems should be solved.

Notebook and reports. The exact type of notebook to be kept and the form of report to be made differ with each laboratory. However, the basic principles involved in all notebook entries and reports are the same, namely: (a) the entries should record observations and conclusions as they are made, so that the notebook may give a clear summary of the work accomplished; (b) the report should be an abstract of the entries made in the notebook with particular emphasis on the final conclusions or the solution of the problem. For beginners, in particular, the authors recommend that the following items be covered in the notebook entries for each known or unknown that is studied:

1. The date received and the nature of the material (single class, "general" unknown, or mixture).

2. Results of gross examination, elemental analysis, solubility data, and a list of the probable class or classes.

3. A list of the functional-group tests that are to be made, together with the results of those tests.

4. A summarized argument, prepared with care as to both grammatical form and logic, regarding the probable nature of the compound, and based on the data collected (including one or more physical constants and a comparison of these constants with the data found in the tables).

5. A list of the types of reactions that can be used for the preparation of derivatives of the probable compound.

6. A summary of the method used in the preparation of the derivative, including the equations for the reactions, the exact methods of purification of the derivative, and the reasons for using the methods chosen.

7. A comparison of the data on physical constants of the original compound and the prepared derivative with data for known compounds taken from the tables.

8. A statement of the conclusions as to final identity.

Nomenclature. In numerous cases as many as half a dozen chemical synonyms may be found for the same chemical compound, several of them having gained extensive use in chemical literature, in books as well as in journals. The authors have deemed it advisable to adopt that terminology which appears to be most widely used in the contemporary chemical literature of the United States, and for this reason every effort has been made to adhere to the system of nomenclature followed by *Chemical Abstracts.* In a few cases, however, it was difficult to ascertain what name was used in *Chemical Abstracts.* In some others the usage seemed inconsistent. An attempt was made (and later abandoned), during the construction of the tables, to include a column for listing synonyms, particularly the modern nomenclature; for example, *Diethyleneglycol diethyl ether* is listed by *Chemical Abstracts* as *Bis(2-ethoxyethyl)ether.* The authors feel that the latter name is more consistent with modern chemical nomenclature, but on the other hand recognize that the name *diethyleneglycol diethyl ether* is preferred by many workers in industry. Although both the modern and older names should be given in separate columns for each compound listed in the tables of derivatives, such procedure would obviously involve a far too ambitious task for a work of this type. Therefore in some instances the synonym of a compound is listed in parenthesis after the name chosen. Some idea of the problem involved may be indicated by the following two examples. The compound *p*-$CH_3C_6H_4CH(OH)CH_3$ is listed by most texts of organic chemistry as ***methyl-p-tolylcarbinol*** or as ***p-tolylmethylcarbinol.*** The compound cannot be found in the index of *Chemical Abstracts* under either of the two names but instead, is listed, as ***p,α-dimethylbenzylalcohol.*** How-

ever, the abstract cited by the index gives the name of the compound as *p-tolylmethylcarbinol* with no reference to its synonym; the original article abstracted appeared in the *Journal of the American Chemical Society;* the name for the compound is *p-tolylmethylcarbinol.* Likewise the compound $C_6H_5CH_2C(OH)(CH_3)_2$ appears in the index of *Chemical Abstracts* as *α, α-dimethylphenethylalcohol,* whereas in most other literature it is still called *benzyldimethylcarbinol.*

For possible changes and additions—particularly for corrections in the physical constants of the compounds listed, new additions, and new derivatives—the authors will appreciate suggestions from all those who are interested in this undertaking. Such communications, which the authors earnestly solicit, may be sent to them in care of the publishers.

CHAPTER 2

Semimicro Laboratory Techniques in Purification of Organic Compounds and Determination of Physical Constants

PURIFICATION of an unknown organic material entails knowledge of the techniques used in crystallization, distillation, and determination of melting and boiling points. In addition, the preparation of derivatives for the final proof of the identity of the unknown consists to a large extent of crystallizations and determination of melting points. Although the reader may be familiar with such manipulations, it is considered appropriate to give a detailed treatment of the semimicro procedures for these laboratory operations, since the latter are not as yet in general use.

The first step in the systematic identification of an unknown is to determine whether the material is a pure substance or a mixture. If the unknown is a crystalline solid, it is examined by means of a magnifying glass or under the microscope to determine whether it has a homogeneous appearance. The melting point of the crystalline material is determined, a small amount is recrystallized, and the melting point is redetermined. If the crystalline solid has a homogeneous appearance and the temperature difference between the two melting points is within 1°, it is considered a relatively pure substance. When the difference is greater and several successive crystallizations fail to give a constant melting point, the unknown is treated as a mixture, as outlined in Chapter 14.

If the unknown is a liquid, a small sample is subjected to simple distillation. If the entire sample distills within a temperature range of 1°–3°, it is assumed that, excluding the presence of azeotropic mixtures, the unknown is a pure substance. Another method is to collect the first and last fractions of the distillate separately; the refractive index of each of the two fractions is determined, and, if the values are nearly the same, the liquid may be considered a relatively pure substance. When the temperature rises slowly during the distillation, the unknown is classified as a mixture. If, on distillation, the temperature rises at first, then remains relatively stationary while a considerable amount of distillate is collected and the residue in the distilling vessel is small, then the unknown is tentatively regarded as a commercial or technical grade of an organic compound.

Crystallization

Organic compounds as prepared from reactants are generally impure even if the initial materials were pure. This situation results from the fact that in most cases side reactions give rise to impurities. Consider, for example, the reaction between methanol and 3,5-dinitrobenzoyl chloride. Assume that a millimole of the acid halide is heated with an excess (3 millimoles) of the alcohol. The usual procedure is to heat the mixture for 5–10 minutes and then add water to separate the solid ester. The ester thus obtained contains a small amount of 3,5-dinitrobenzoic acid and traces of its anhydride, which will cause a depression of several degrees in the melting point of the solid ester. The formation of the acid results from: (a) a small amount of water present in the methanol; (b) moisture absorbed by the halide from the walls of the vessel and from the air while it is weighed; (c) the action of water on the unreacted halide, since, in most cases, the conversion of the alcohol to the ester is not complete. It is a common practice to remove the small amount of dinitrobenzoic acid by washing with a dilute solution of sodium hydroxide or sodium carbonate. The rate of solubility is not rapid at ordinary temperatures, and, if the mixture is heated to accelerate the solubility, hydrolysis of the ester may occur, thus forming more dinitrobenzoic acid. Therefore the crystalline ester is washed and then purified by *crystallization* from an appropriate solvent.

The term *crystallization* means the deposition of crystals from a solution of a substance or of a mixture of substances. As generally used in organic chemistry, the term denotes dissolving a solid by heating it in an appropriate solvent (such as methanol, ethanol, water, benzene, and the like), filtering off any undissolved impurity, and causing the separation of crystals by cooling the solution.

Solvents. The choice of the solvent in the crystallization of derivatives is of extreme importance. In most cases the solvent cannot be selected on the basis of rules or theoretical considerations, but must be experimentally determined, and therefore for recommended derivatives the solvent is specified.

The literature describing derivatives contains a reference to the solvent used but very seldom to the solubility data. In such cases the beginner should proceed cautiously to determine roughly the solubility as described below. The following general rules with reference to solvents will be valuable to the beginner:

1. A solid usually dissolves best in a liquid that it resembles in struc-

ture. For solid esters solvents such as methanol, ethanol, and ethyl acetate should be among the first to be tried.

2. It is advisable to select a solvent that will dissolve the crude solid when hot, but only sparingly when cold.

3. When a solvent dissolves a solid very readily in the cold, it may be useful as a crystallizing medium if it is mixed with another solvent in which the compound is sparingly soluble. Thus, if a substance is very soluble in alcohol in the cold and sparingly soluble in water, it is dissolved in a small amount of hot alcohol, the solution filtered, and then precipitated by cautiously adding water until cloudiness develops. The use of *solvent pairs* is very helpful in many crystallizations.

4. The impurities present should either be very readily soluble or as sparingly soluble as possible in the solvent. For example, in the 3,5-dinitrobenzoates ($C_6H_3(NO_2)_2COOR$) used for the identification of hydroxy compounds, the impurity (dinitrobenzoic acid) is completely soluble in methanol or ethanol used as a solvent for the crystallization. Another derivative for hydroxy compounds may be prepared by allowing the alcohol to react with an isocyanate such as phenyl isocyanate (C_6H_5NCO). The desired derivative is known as the *urethan*, $C_6H_5NHCOOR$, and the impurity is diphenylurea, $C_6H_5NHCONHC_6H_5$, produced by the action of moisture present in the hydroxy compound or on the walls of the vessel. Hot petroleum ether dissolves the urethan but not the diphenylurea.

5. The solvent should be chemically inert to the compound to be crystallized. In some cases, however, a solvent may be chosen because it reacts chemically with the compound. For example, some aromatic acids may be purified by dissolving in dilute sodium hydroxide and then, after filtration of the solution, precipitated by neutralization with dilute hydrochloric or sulfuric acid.

6. In the event that a solvent is not given in the literature, it is recommended that the procedure outlined below be tried with solvents in the following order: methanol or ethanol, mixture of lower alcohols and water, acetone or mixture of acetone and alcohol, benzene or mixtures of benzene and toluene, petroleum ether or benzene and petroleum ether, glacial acetic acid or aqueous acetic acid. Table I shows a number of solvents and solvent-pairs used for crystallization of derivatives. The general procedure for the preparation of solvent-pairs is to use a solvent in which the derivative is most soluble and then, after the solution has been prepared, to add cautiously a solvent in which it is least soluble. The two solvents must be miscible and should be used hot.

Proper solvent and amount. If it is impossible to determine through the literature what solvent to use, or if the solvent is known but not the amount to be used, the solubility of the derivative should be determined roughly. About 50 mg of the solid are placed in a small test tube (3–4 inch) and, by means of a graduated pipette, 0.5 ml of the solvent added

TABLE I

Common Solvents for Crystallization of Derivatives

Solvent or Solvent Pair	Useful Derivatives
Water	Carboxylic acids, amides, and substituted amides
Methanol	Most derivatives: benzoates, 3,5-dinitrobenzoates, amides, *p*-toluidides, nitro and bromo compounds, etc.
Methanol-water	*p*-Nitrobenzyl esters, sulfonamides, anilides, picrates, semicarbazones, hydrazones, substituted hydrazones, etc.
Ethanol	Same as methanol and methanol-water mixtures, molecular complexes
Dioxane-water	Xanthylamides
Petroleum ether	Phenylurethans, α-naphthylurethans
Petroleum ether-benzene	*p*-Nitrophenylurethans, 3,5-dinitrophenylurethans
Acetone-alcohol	Osazones, bromo compounds, nitro compounds
Isopropyl ether	Quaternary ammonium salts
Ethyl acetate	Quaternary ammonium salts, esters
Benzene	Picrates, molecular complexes
Chloroform and Carbon tetrachloride	Sulfonyl chlorides, acid chlorides, anhydrides

and the tube shaken vigorously. If the solid dissolves completely, the solubility at room temperature is above 100 mg per milliliter of the solvent. Such a solvent used alone is not useful for crystallization. If the solid does not dissolve, successive portions of 0.5–1.0 ml of solvent may be added, the tube being shaken after the addition of each portion, until the solid dissolves. The number of milliliters of solvent used divided into

50 gives the number of milligrams of solid dissolved by each milliliter of solvent at room temperature.

The solubility of the solid at or near the boiling point of the solvent is determined by a similar procedure. After the addition of the first 0.5 ml of solvent, the tube is cautiously heated until the solvent just begins to boil. If the solid dissolves completely, the test is repeated, 0.3 ml of solvent being used. If some of the solid remains undissolved, more solvent is added in portions of 0.2–0.3 ml, the tube being heated after the addition of each portion. In this manner the solubility of the solid at or near the boiling point of the solvent and also at room temperature is determined. This information is used to determine the solvent and the amount to be used. Let it be assumed, for example, that 8 ml of methanol were used to dissolve 50 mg of a derivative at 20° and 0.9 ml at the boiling point of alcohol. The solubility, therefore, at 20° is about 6 mg per milliliter and, at or near the boiling point of methanol, 55 mg per milliliter. If the amount of derivative to be crystallized is 200 mg, the amount of methanol to be used is 4–4.5 ml. After crystallization about 25 mg of the derivative will remain in the mother liquor. Generally the solvent is not particularly useful unless the solubility near the boiling point of the solvent is *at least 5 times the solubility at room temperature.* If, in the above example, the solubility at room temperature was found to be 12 mg per milliliter, the loss will be at least 50 mg in the first crystallization.

The solubility tests, both at room temperature and at the boiling point of the solvent, can be performed by using 5–10 mg of the solid; the solvent is measured by means of a dropper (see pages 76–77).

The solvent used most extensively in the experimental part of this work is methanol. Wherever possible, the crude derivative is dissolved in methanol and precipitated after filtration by cautious addition of water. Although methanol is toxic when absorbed in the tissues in appreciable quantities, the handling of small amounts by beginners has been found entirely safe provided caution is used. A number of other factors make the use of methanol more desirable than ethanol. In general the solubilities of organic compounds are not greatly different in the two homologs. The commercial grade of methanol is almost anhydrous and of greater purity than the commercial grade of ethanol. In addition, the ease with which methanol is obtained in the market, plus its low price, makes its use desirable wherever possible.

Solution. Since it is assumed that the reader is familiar with general directions for effecting the solution of a solid in a solvent, only brief directions will be given as applied to the use of semimicro techniques.

The most useful vessels for effecting the solution of 100–500 mg of an organic compound are test tubes. The size of the test tube depends on the amount of solid to be crystallized. The preparation of derivatives as outlined in the procedures described in this book are performed for the most part in 8-inch test tubes. These same test tubes may be used directly for effecting solution of the impure derivative. If the amount of solvent to be used is less than 5 ml, a 6-inch tube (20 x 150 mm) is preferable. For amounts of 10–30 ml, 8-inch tubes (25 x 200 mm) are used. Small flasks of 25–50 ml capacity may be used, but they cannot be cleaned so easily as test tubes. If flasks are used preference is given to the pear-shape type particularly when the amount of solution is small.

FIGURE 1

Apparatus for Heating under Reflux

The compound to be crystallized is placed on a piece of shiny paper (50–60 mm in width and 75–100 mm in length), creased at the middle to about one half its length. The paper containing the crystals is held at the edges by the thumb and the index finger and is tilted so that the crystals roll through the creased end into the mouth of the tube. By means of a pipette dropper the appropriate amount of solvent is added to the upper (inner) part of the tube in order to wash down the crystals adhering to the sides of the vessel. In absence of graduated pipette droppers, it is advisable to measure the solvent in a 10-ml graduate and remove successive portions by means of an ordinary dropper. In this manner the amount of solvent added is controlled. The solvent may also be measured by means of ordinary droppers as outlined on page 76. The tube is inclined at an angle of 65–75°, with the mouth directed away, and is moved gently over a small flame of a microburner. Since most organic solvents are inflammable, the question of whether the beginner

should use a water or steam bath is of some importance. It has been found by the authors that in dealing with small amounts of solvent it is possible with a little care to avoid accidents. The vessel should never be more than one third full; the flame should be directed first at the top of the liquid layer and then slowly moved downwards. If complete solution of the solid is not effected when the liquid just begins to boil, then more solvent is added. Finally, when the solid dissolves slowly or the amount of solvent exceeds 10 ml, the apparatus shown in Figure 1 is used. This arrangement provides for effecting solution by heating under reflux.

Filtration of solution. The apparatus found most useful for filtration of semimicro quantities is shown in Figure 2. The funnel[1] has a diameter of 50 mm at the top, with a stem 55 mm long. The inside of the funnel and about 30 mm from the top is slightly etched or ground so as to produce a band 5–10 mm wide. A porcelain perforated disc[1] 20 mm in diameter and 5 mm in thickness fits inside the funnel against the ground band. The edges of the disc are beveled so that the bottom diameter is about 15 mm (Figure 2). The funnel fits through a one-hole No. 4 rubber stopper into the mouth of an 8-inch tube having a side arm. The end of the funnel stem protrudes 10–12 mm below the side arm, which is connected to a rubber hose leading to an ordinary water aspirator. In the absence of a water aspirator it is connected to a rubber aspirator bulb.

To prepare the funnel for filtration, the tube is placed on a test-tube rack or clamped to a small stand. The perforated porcelain disc is dropped inside the funnel and arranged in place by a slight pressure of the finger. A disc of filter paper 24–25[1] mm in diameter is placed on top of the porcelain; by means of a pipette dropper two drops of water are placed on two different parts of the surface of the paper and the funnel tilted slightly so that the filter paper is moistened throughout. The funnel is fitted into the mouth of the receiving tube, which in turn is connected to the aspirator. By applying gentle suction the filter paper is sucked down in place. If the filter paper is properly placed, the edges are held tightly against the funnel and protrude upward. If any part of the paper protrudes downward, a leak will develop during filtration; in such a case the suction is discontinued, another drop of water is added, and the filter paper is adjusted with a spatula. After the filter paper has been made to adhere to the sides of the funnel, the suction is momentarily discontinued, 2 drops of methanol are added to the paper, and suction is applied again. The receiving tube is changed, and the

[1] Wilkens-Anderson Co., Chicago, Ill. Apparatus No. 3970-G; 6305-BE.

funnel is ready for filtration if the solvent is an alcohol, ether, ester, or an organic acid. When a hydrocarbon, such as benzene, heptane, and the like, is used as a solvent, the moistening of the paper by water is followed by washing with acetone and then with 5–6 drops of the hydrocarbon; then suction is applied.

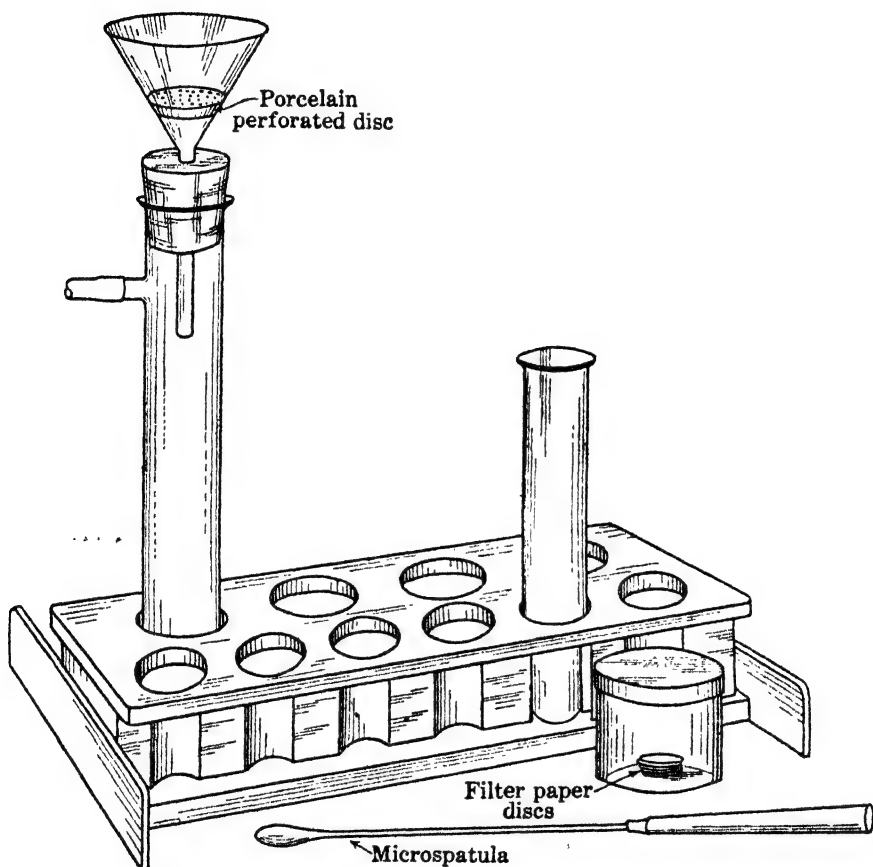



FIGURE 2
Apparatus for Semimicro Filtration

The funnel prepared as described in the preceding paragraph is fitted into the mouth of the tube, and gentle suction is applied through the side arm. The tube containing the hot solution is held by one hand and its mouth is lowered over the funnel so that the solution is poured through the center of the disc. It is advisable to use a glass rod in pouring the hot solution into the funnel. The tube containing the solution is lowered so that it just touches a rod held vertically with one end touching the

filter disc. The filtration is complete within a few seconds. If the amount of the solid being crystallized is very small, 0.5 ml of fresh solvent is added to the tube from which the solution was poured out and heated until all the crystalline solid adhering to the sides is dissolved; the hot solvent is then poured into the filter so as to wash down any solid adhering to it.

The funnel is removed and cleaned immediately and then set aside, upside down, to drain and be ready for the next crystallization. The tube containing the filtered hot solution is immersed in a beaker or a small jar in which running tap water circulates; the solution is stirred with a glass rod from time to time. For most derivatives 5–10 minutes of cooling is sufficient; others require 15 minutes or more for complete crystallization.

If mixed solvents are used, such as alcohol (methanol or ethanol) and water, it is advisable to effect solution in alcohol and after filtration to add warm water dropwise by means of the pipette dropper until a permanent cloudiness is obtained on shaking. The tube is heated until the cloudiness disappears and is then cooled.

Filtration of crystals and recrystallization. The crystals and mother liquor are thoroughly stirred by means of the rod so as to loosen most of the solid adhering to the walls of the tube. A clean eight-inch tube with side arm is fitted with the filter funnel prepared as described in the preceding paragraph. The tube is shaken two or three times and the contents are poured into the funnel. The mother liquor is poured back into the crystallizing tube, and the process is repeated until practically all the adhering crystals have been transferred into the funnel. The draining is complete within a minute or two. About 0.5–1 ml of solvent is added to the tube in which the crystallization took place, and the tube is shaken so that washing of the adhering crystals takes place, since the tube is to be used directly for the second crystallization. The amount of solvent added should be insufficient to dissolve the crystals remaining in the tube. The suction is discontinued, and the washings are added slowly over the crystals in the filter so that the entire mass is moistened; after a minute the washing is repeated. The filtrates are saved until the crystallization is complete, and the melting point determined.

The funnel is removed from the tube, and, by means of a spatula, a small amount of crystals (5 mg) is placed on a marked section of a paper drying disc or porous microplate.[2] The paper disc has a diameter of 90–100 mm, and the plate is 50 x 50 mm; with a pencil it is divided into four

[2] **Wilkens-Anderson Co., Chicago, Ill., disc: 6354; plate: 4444; A. H. Thomas Co., Philadelphia, Pa.**

equal sections labeled with numbers to represent the successive crystallizations. The filter paper containing the crystals is loosened with the spatula and transferred directly into the 8-inch tube in which crystallization took place. If this manipulation is difficult for the beginner, the funnel may be placed mouth downward on a small piece of clean paper, and, by a slight pressure with the spatula, the porcelain disc and the crystals are made to fall on the paper. The porcelain disc is pushed out with the spatula, and the crystals, together with the filter paper, are transferred into the crystallizing tube. The amount of solvent to be added varies between 50 per cent and 80 per cent of the amount used in the first crystallization. Assume that 7 ml of methanol were used in the first crystallization. Since a certain amount of the solid remains in the mother liquor, depending on the solubility of the derivative, it is advisable to begin with 4–5 ml of methanol for the second crystallization. The tube is heated until the solvent begins to boil; by means of a spatula or a glass rod the filter paper is pulled up on the sides about 50 mm from the bottom and the heating is resumed, so that the hot vapor condenses on the region of the filter paper and washes down any adhering solid. The filter paper is pulled out and discarded. Additional solvent is added until the solid dissolves at a temperature near the boiling point of the solvent. If proper care has been taken, the solution will be clear and without shreds of paper, so that filtration of the solution may not be necessary; if the solution is not clear, it should be filtered, using the same procedure as before. The cooling of the hot solution and filtration of the crystals are accomplished in the manner already described. A sample of the crystals (5 mg) is removed and placed on a marked portion of the paper drying disc or drying plate on the opposite side from the sample of the first crystallization.

When two crystallizations have been completed, the melting point of the dry crystals is determined. If the melting points of the crystals from two successive crystallizations are identical or within 0.5° of each other, the derivative may be regarded as pure. In any case the bulk of the crystals from the second crystallization is saved until the identification of the compound is complete. For this purpose it is not unusual to make the same type of derivative, starting from a known sample of the compound that has been tentatively identified. For a discussion of mixed melting points the reader is referred to page 39.

Additional filtration apparatus. A variety of arrangements have been used for semimicro and micro filtration, and the reader is referred to the literature section at the end of the chapter. A small Buchner funnel, 15 mm in diameter, 10 mm in depth, and with a 35 mm stem,

which is made by the Coors Porcelain Company, is available through laboratory supply dealers. In the opinion of the authors it is not so convenient for filtering and cleaning as the arrangement with the porcelain disc, in addition to being more costly.

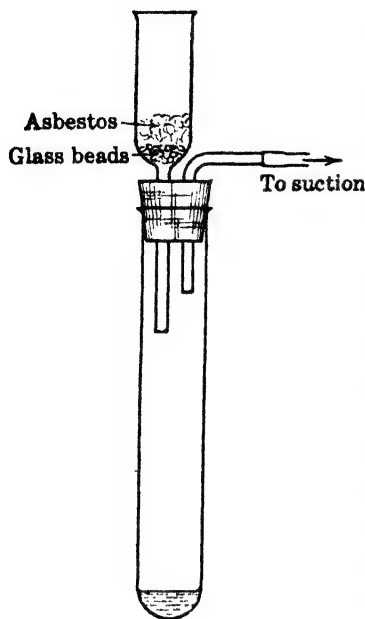



FIGURE 3
Semimicro Apparatus for Suction Filtration Using Filter Tube

A filter-tube arrangement is shown in Figure 3.[3] The filter tube can be easily made in the laboratory from ordinary 5-, 6-, or 8-inch test tubes, depending on the size desired. The test tube is heated in the flame until it is soft and then drawn out slowly for about 100 mm. After the tube has cooled, the drawn-out part is cut so as to provide a stem of 70 mm. The stem is then fire-polished. The upper part of the tube is flared open by heating and then smoothing out with the round handle of a file. Two or three small pieces of glass are placed in the neck of the filter, and then small glass beads, to make a layer of about 4–5 mm. The glass beads are made by heating a glass rod of 6 mm and then immersing it in a small beaker containing cold water. The filter is now inserted through one opening of a two-hole No. 4 rubber stopper; a short L tube serves as a side arm for attachment to a suction pump. The filter is fitted to a 6-8-inch test tube, and the latter is clamped to a stand. A small amount of asbestos fiber pulp or filter paper pulp is added and sucked dry. The thickness of the filter mat should be about 2–3 mm. A clean receiving tube is inserted, and the apparatus is ready for filtration. When filtration is finished and the filter tube is cleaned immediately, the filter mat is removed by means of a spatula, and the filter with the glass beads is cleaned by washing first with 5 cc of the solvent, then with water, and rinsing with a little cleaning solution. Finally, it is washed with water again and a new filter mat inserted before putting it away. It is advisable to prepare several of these filter tubes, for even though the method is a bit laborious, it is satisfactory when other equipment is not available.

When a centrifuge is available, it can be adapted for filtration by using the centrifuge tubes shown in Figures 4*A* and 4*B*. The sizes of

[3] Wexler, *J. Chem. Educ.*, **18**, 167 (1941).

the centrifuge tubes may vary. The centrifuge tube shown in Figure 4*A* is 110–120 mm in length and 12–15 mm in diameter, constricted to 2–3 mm in the middle to permit insertion of a filter mass plug. The end of the tube is shaped for stoppering with a small rubber cap or

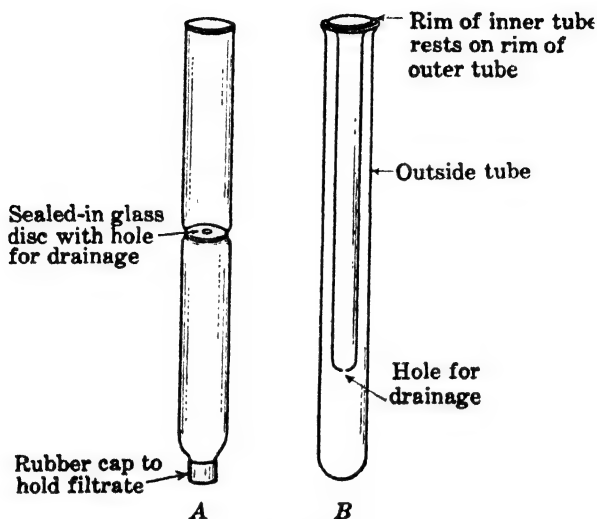



FIGURE 4
Centrifuge Tubes

rubber stopper. A small plug of paper filter mass is tapered and placed in the constricted opening at the middle of the tube. A few drops of water are added, and the mass is pressed with the flat end of a glass rod to spread it on the opening. The tube is then centrifuged for 15 seconds, when it is ready for use.

The mixture of crystals and solvent to be filtered is added to one tube, and an equal amount of solvent is added to a second centrifuge tube with no filter mass. The tubes are then centrifuged from 1–2 minutes. The stopper at the lower opening is removed and the filtrate drained to a test tube for future reference. A few drops of solvent are added and the tube centrifuged for one minute. This process is repeated once more. For rapid drying, the washings are drained, and the tubes are again centrifuged for 2–3 minutes, thus removing the adhering solvent and traces of mother liquor. The crystals are removed to a drying disc by means of a spatula.

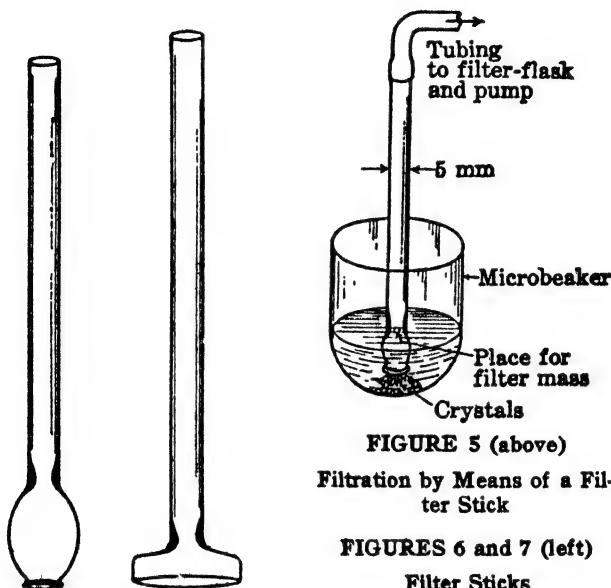
Figure 5 shows the arrangement of apparatus for filtration by means of a filter stick. A filter stick is a short tube constricted about 10 mm above one end and then flared so as to produce a small well. Two types

of filter sticks are shown in Figures 6 and 7. The model[4] shown in Figure 6 may easily be made from glass tubing 5–6 mm in outer diameter. A piece 22 mm long is heated just above the blue cone of the flame while being slowly rotated around its axis. As the glass softens, it is gently pushed together so as to thicken the plastic region. It is then removed from the flame and drawn out slightly so as to form a capillary of about 1 mm bore and 10–15 mm length: Figure 8*A*. The tube is heated as

FIGURE 5 (above)

Filtration by Means of a Filter Stick

FIGURES 6 and 7 (left)

Filter Sticks

before about 10 mm from the capillary in order to draw out a second capillary with a bulb between the two as shown in Figure 8*B*. The flame of the burner is adjusted to a short cone, and the capillary (*C*) is drawn out so that the bulb remains closed as shown in Figure 8*D*. The bulb is now heated and slowly blown into the shape shown in Figure 8*E*. The thin glass is knocked off, and the bulb is heated, then pressed firmly downward on a piece of asbestos. A well is formed having a diameter of 8–10 mm at the rim and a depth (up to the constriction) of 15–20 mm.

A filter mat made from wet filter paper pressed together or from asbestos fiber is inserted in the well and pressed at the lower end of the filter stick, which is connected as shown in Figure 5. A small amount of solvent used in the crystallization is placed in a tube and the filter stick immersed in it. Light suction is applied, and the solvent is allowed to

[4] Benedetti-Pichler: *Introduction to the Microtechnique of Inorganic Analysis*, John Wiley and Sons, Inc., New York, 1942, pp. 202–204.

pass through. The filter stick is then ready for filtration. The filter stick is useful for handling a few milligrams of crystals.

Crystallization of microquantities. In research work it often becomes necessary to purify by crystallization of 0.5–5 mg of substance. Such crystallizations may be accomplished either in capillaries or in glass slides. For crystallization in capillaries the reader is referred to the literature;[5] the described method gives satisfactory results after some practice. For the beginner the glass-slide method offers an opportunity to acquire technique in handling microquantities before attempting crystallization

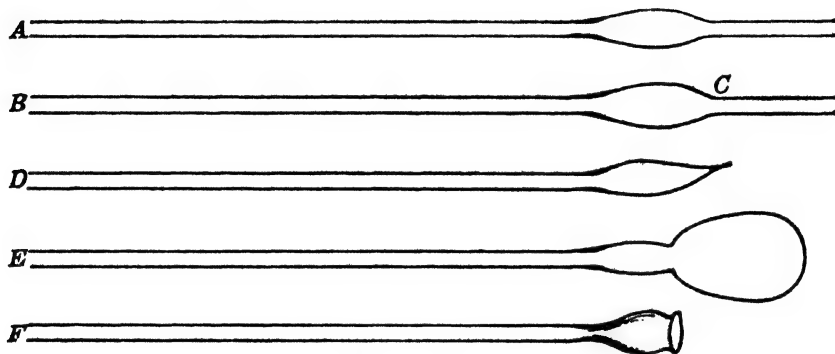



FIGURE 8

Steps in the Construction of a Filter Stick

in capillary tubes. A convenient microscope glass slide for beginners is about 75 mm in length and 25 mm wide, with a circular depression of 15–17 mm in diameter. The substance to be crystallized is placed in the depression by means of the microspatula and 2–3 drops of the appropriate solvent are added by means of a capillary pipette dropper. The capillary pipette may be calibrated to deliver 0.3–0.4 ml, which is the maximum capacity of the glass depression. The slide is heated by passing carefully over a microflame until the crystals dissolve. If alcohol is used as a solvent, a very small amount of water is added to the warm solution by means of the capillary pipette until a cloudiness appears; the slide is heated again and then cooled by placing it across a 25 or 50 ml beaker full of ice water. If a certain amount of the solid has remained undissolved, the warm solution is drawn rapidly into a clean capillary pipette that has been previously warmed by passing over a microflame and transferred at once to another slide and cooled.

When crystallization is complete, the crystals are pushed to one side

[5] Emich-Schneider, *Microchemical Laboratory Manual*, John Wiley and Sons, Inc., New York, 1932, pp. 31–32 and 127–129; Pregl, *Mikrochemie*, **2**, 76 (1924).

by means of the microspatula. While the glass slide is held between the thumb and the index finger and rests on the second finger of the left hand, it is tilted so that most of the liquor collects at the end of the depression away from the crystals; by means of a capillary pipette having a fine point most of the liquid in the depression is withdrawn. The residual mother liquor is then removed by pushing the point of a triangular filter paper into the depression. Next the crystals are washed by addition of small amounts of a solvent pair; for example, if alcohol is used for crystallization, two drops of a mixture of 25 per cent methanol and 75 per cent water are used. The washing liquid is removed as described above. The washing may be repeated, after which the crystals are transferred to a drying plate where, if necessary, another washing may be performed by adding 1–2 drops of the mixed solvent on the crystals.

An ordinary glass slide or cover glass (without the depression) may be used for crystallization of quantities less than 0.5 mg. First, the solid is placed on the slide and then a drop of the appropriate solvent placed on it. The slide is heated carefully by passing it several times over a microflame until no more solid dissolves. With the slide slightly tilted the warm solution is drawn into a clean capillary pipette that has been warmed and transferred rapidly to another part of the same slide. When crystallization is complete, the mother liquor is removed as described in the preceding paragraph except that the quantities of solvent used for washing are much smaller. Final drying of the crystals may be effected without removal from the slide, thus reducing the losses due to handling and transferring, by passing the slide over the microflame several times.

Drying of crystals. The 5–10 mg samples of derivatives required for the determination of melting points dry rapidly on the paper drying discs or porous drying plates while additional crystallizations are being carried out. If the melting points are to be determined on the following day, the crystals are covered with a watch glass, and the disc is placed carefully in a cupboard or on a shelf. When rapid drying is desired, the disc or plate is placed on a watch glass resting on a tripod or ring stand and heated by a very small flame from a micro burner. The crystals are turned over with the blade of the micro spatula. If the substance shows signs of melting, the drying disc is lifted momentarily from the dish and the flame lowered. Complete drying is indicated when none of the crystals adhere to the blade of the spatula on being turned over.

In some cases drying in a desiccator may be necessary. A hand desiccator is shown in Figure 9. It consists of a small, wide-mouthed, glass-stoppered bottle of about 60-ml capacity. The drying agent is placed in

the lower part of the bottle at a depth of about 10–15 mm. The sample is placed in a small tube or vial whose upper part, when placed within the bottle, reaches about 5–10 mm below the mouth of the bottle. The hollow stopper of the bottle is smeared with a thin coating of stopcock grease before stoppering the bottle. The drying agent depends on the

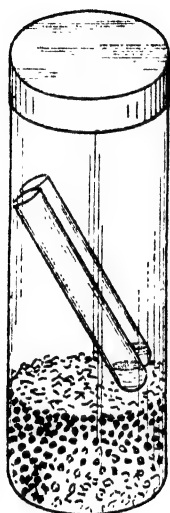



FIGURE 9
Desiccator Bottle

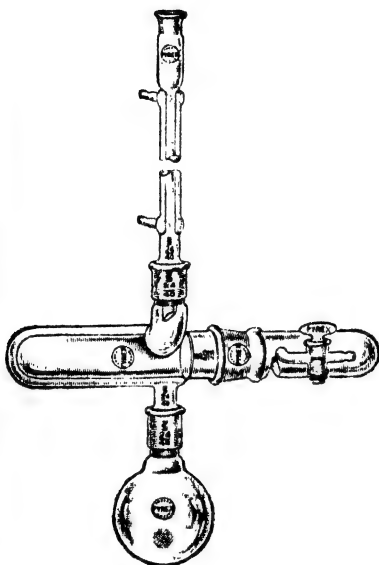



FIGURE 10
Pyrex Vacuum Drying Apparatus

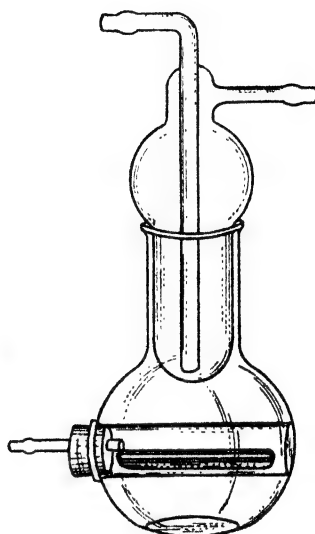



FIGURE 11
Benzamin Vacuum Drying Apparatus

nature of the solvent used for crystallization. A mixture that will be satisfactory for most purposes consists of 5 g of sodium hydroxide pellets and 5 g of anhydrous calcium chloride (8 mesh). If a hydrocarbon was used as the crystallizing solvent, a few pieces of freshly cut paraffin wax are added to the bottle. When the solvent is of an alkaline nature, a small tube containing concentrated sulfuric acid is placed by the side of the tube containing the crystals. In most cases 100 mg of crystals placed in such a desiccator dry overnight. The tube is lifted out with forceps and held upright until its lower part has been wiped thoroughly dry; it is then tilted so that the dry crystals may be emptied out onto a clean watch glass or paper. The familiar vacuum desiccator is used for large samples, particularly when it is desirable to dry crystals efficiently. To open an exhausted desiccator, turn the stopcock gradually so as to admit the air very slowly; this prevents the dried substance from being blown out of the container.

Figures 10 and 11 show two types of commercially available glass

apparatus[6] for drying micro and semimicro quantities of crystals under reduced pressure at constant temperature. The apparatus shown in Figure 10 consists of four parts connected by three standard ground glass joints. The boiling flask is connected to the heating chamber which has a jacketed inner tube in which the sample to be dried is placed. The heating chamber is connected to a condenser and a drying chamber which has a depression for the desiccant, and an outlet for connection to a vacuum pump. The heating chamber is maintained at constant temperature by the vapors of a liquid, which is heated in the round bottom flask. By using different liquids a wide range of temperatures may be obtained.

FIGURE 12

Test-tube Vacuum Micro-desiccator

Figure 11 shows a less expensive apparatus which utilizes the same principle, as the apparatus shown in Figure 10. The boiling flask is a 500 ml Pyrex extraction flask with a 25 mm heating tube sealed about the middle with one end closed and the other open and flared so that a stopper with a stopcock can be inserted. A cold finger condenser 35–40 mm in diameter fits over the mouth of the flask. The crystals to be dried are placed inside of a tube or boat and then inserted into the short horizontal chamber; the desiccant is placed into a three-inch tube and then inserted into the heating chamber. It is advisable to have the tube containing the desiccant with the mouth facing the opening of the heating chamber and the tube containing the crystals to be dried with the mouth facing the closed end.

Figure 12 shows an inexpensive vacuum desiccator which is easily assembled and well adapted for the drying of most derivatives prepared by the beginner. It consists of a 20 x 150 mm Pyrex test tube having an empty litmus paper vial at the bottom. Above the mouth of the open litmus vial which contains the desiccant and about the middle of the test tube a plug of glass wool is placed. The glass wool supports a small vial or tube (10 x 35 mm) which contains the crystals to be dried. A number 3 rubber stopper holding a stopcock fits into the mouth of the test tube and serves for connection to the vacuum pump. The test tube desiccator

[6] Apparatus shown in Fig. 10: Pyrex No. 3690; apparatus shown in Fig. 11: E. H. Sargent and Co., Chicago; Benzamin drying apparat No. S-28847.

is placed in a rack after evacuation and allowed to stand at room temperature or it can be heated in a bath, (below the melting point of the crystals).

The desiccant to be used depends on the solvents employed for crystallization and washing of the crystals. A mixture of calcium chloride and sodium hydroxide pellets and a few small pieces of paraffin wax serves as absorbents for most of the common solvents. Other desiccants which may be used are: phosphorus pentoxide, "Drierite," sulfuric acid and soda lime.

Determination of Melting Points

The melting point of a pure solid organic compound is used as a criterion of its purity. In the identification of organic compounds the melting point of the derivative that is prepared serves as the most important constant in the proof of identity.

For the determination of melting points the *capillary-tube* method is commonly used. About a milligram (or less) of the solid is placed in a thin glass capillary tube having a diameter close to 1 mm. The capillary tube is attached to a thermometer, then placed in a liquid bath, and heated slowly. The interval of temperature in which the solid within the capillary tube begins to liquefy and the temperature at which the liquid is clear is recorded as the *observed melting range*. It should be noted that melting points determined by this method are not *true melting points* but *capillary melting points*; the latter are slightly higher than the true melting points, which are determined by cooling or heating curves;[7] these require larger samples but give more exact information as to the purity of the compound. Hence for all ordinary purposes the capillary-tube method is used. The amount of substance required for a single determination by the capillary-tube method is usually 1–2 mg, although a fraction of this amount may be used. By the use of a microscope to observe the melting point, a few crystals weighing a fraction of a microgram (1×10^{-6} g) will suffice for the determination.

The accuracy of the determination of melting points by the capillary-tube method is influenced by several factors, of which the most important is the thermometer stem correction for the mercury column above the surface of the bath. As discussed on pages 32–33, it is possible to calibrate the thermometer in terms of melting points of very pure crystalline

[7] Skau and Wakeham, in Weissberger, *Physical Methods of Organic Chemistry*, Vol. I, Interscience Publishers, Inc., New York, 1945, pp. 8–19.

substances, and apply a correction to the observed melting-point temperature range. The values that are obtained in this manner are known as *corrected melting points.* Unfortunately most of the melting points found in the literature are *uncorrected.* However, at present the practice is to report corrected melting points. In connection with the melting points of derivatives, the reader is referred to pages 201–204.

Melting-point tubes. Glass capillaries of uniform diameter (1–1.2 mm) and 70–75 mm in length are commercially available packed in vials, at a cost of about fifty cents per hundred. It is recommended, however, that beginners learn to prepare glass capillaries by heating and drawing out glass tubing that has been thoroughly *cleaned.* A soft glass test tube 12–16 mm in diameter, or any thin-wall glass tube 6–8 mm in diameter and 16–20 mm in length, is rotated in the hottest part of the Bunsen flame. When soft, it is removed from the flame and drawn out slowly in such a manner as to insure a uniform capillary bore; this should be about 1 mm in diameter. The capillary is cut into lengths of 70–90 mm, and one end is sealed by heating for a few seconds in the outside tip of the flame. Care should be taken not to make the sealed end thick. The capillaries are placed in a dry test tube, which is tightly corked to keep out moisture and other impurities.

To load the capillary tube, a few milligrams of the crystalline material are placed on a watch glass or piece of clean paper and crushed to fine powder by drawing the spatula over them. The open end of the capillary tube is pressed into the fine powder; then the closed end is tapped on the desk, or the tube is lightly scratched with the flat part of a file, in order to force the sample to the bottom. The tube is filled to a height of about 1–2 mm and is then attached to the thermometer so that the end of the capillary tube reaches the middle of the mercury bulb. If an oil is used as a bath, the capillary tube is attached to the thermometer by means of a small rubber band cut from ordinary $\frac{3}{16}$-inch tubing. The rubber band is so adjusted that it is near the top of the capillary tube and does not come in contact with the liquid bath. The rubber band has the disadvantage that on heating it may come in contact with the bath liquid and color it, so it is advisable to use new rubber bands for every determination.[8] A fine copper wire wound several times around the thermometer and capillary has been successfully used by the authors. Another method suggested in the literature is to omit the rubber band and attach the capillary by placing a glass rod against the entire length of the thermometer above the bulb; the capillary is fitted in the groove

[8] Silicone fluids do not affect rubber or metal bands; see page 31.

formed by the rod and thermometer. If sulfuric acid is used as a bath the rubber band is unnecessary, as capillary attraction will hold the melting-point tube to the thermometer.

Liquid bath and apparatus. A number of different types of apparatus and liquids are used as heating baths. Four types of melting-point apparatus are shown in Figures 13 and 14*A*, *B*, *C*. Either the beaker or the flask method is convenient. In the beaker method (Figure 13) a glass rod is bent in the form of a loop at one end and a handle at the other. This rod is used as a stirrer by being slowly raised and lowered to insure uniform temperature. A mechanical stirrer placed near the bulb of the thermometer gives more uniform heat interchange. In the flask method (Figure 14*A*) a Pyrex 200–250 ml round-bottom flask with a long neck is used. The thermometer, which is provided with a cork, is so adjusted that the mercury bulb reaches the middle of the liquid in the flask. A section of the cork is cut out to allow vapors of the liquid to escape and also to make the thermometer scale visible at that point. A glass tube 5 mm in diameter reaches almost to the bottom of the flask. The end is drawn into a capillary with a 0.5-mm orifice or less so that a current of air can be blown through the liquid bath. The upper part of the tube is bent at an angle and connects to a piece of rubber tubing of sufficient length so that it can be attached to a rubber bulb by means of which air is forced through the liquid. Air is blown in at frequent intervals at such a rate that it is just possible to count the bubbles. Since there is a tendency for the oil to become cloudy, it is heated occasionally at 130–150° for 15–20 minutes, in order to expel the moisture.

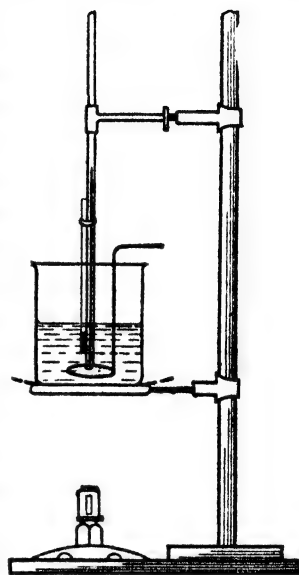



FIGURE 13

Heating Bath (beaker) for Determination of Melting Points

A double-bath apparatus can be easily made by inserting a 16 x 160-mm test tube through the cork of the flask. The tube reaches to within 10–15 mm of the bottom of the flask and contains the same liquid as that used in the bath and the thermometer. This arrangement insulates the thermometer and sample from convection currents.

Figures 14*B* and 14*C*[9] show two modifications of the Thiele apparatus,

[9] Wilkens-Anderson Co., Chicago, Ill. Apparatus No. 8368.

the latter being a variation made by the authors on the modification proposed by Conte. In this apparatus air is blown by means of rubber aspirator bulb at frequent intervals at such a rate that it is just possible to count the bubbles. In this manner very good circulation of the liquid bath is obtained.

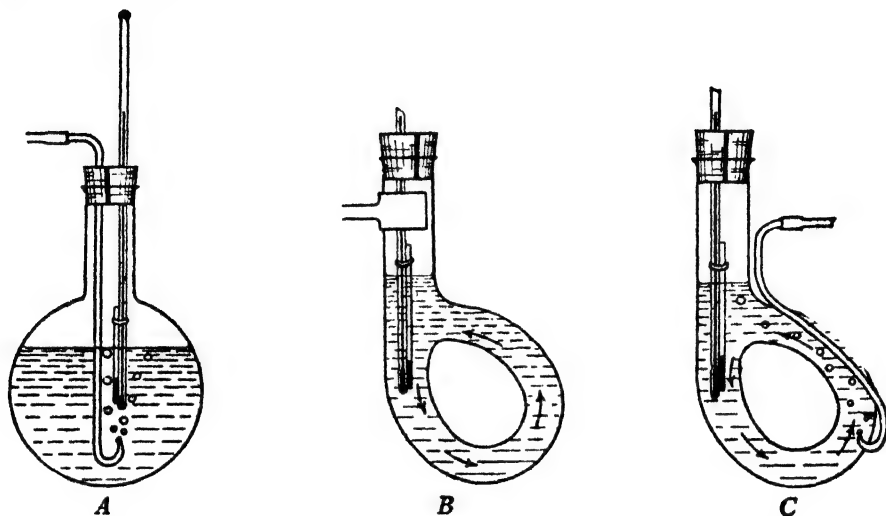



FIGURE 14

Heating Baths for Melting-Point Determination: (A) Flask; (B and C) Modified Thiele Heating Baths

For the determination of melting points up to 230°, a high grade of heavy petroleum (mineral) oil may be used as the liquid for the melting-point apparatus. Concentrated sulfuric acid may be used for determinations up to 300°. A mixture of six parts of acid and four parts of potassium sulfate, which is solid at ordinary temperatures, may be heated up to 365°. There is **great danger** involved in heating sulfuric acid and mixtures of the acid and potassium sulfate; in addition to the danger resulting from breakage, the mixture of acid and salt may separate into two layers and, when heated, mix with explosive violence. In laboratories in which the use of sulfuric acid for heating baths is not permitted, a petroleum wax melting at 60–70° is used for temperatures of 250–350°.

An alternative method is to use a copper or aluminum metal block, of which several models have been described and are commercially available.[10] The ordinary Maquenne type consists of a metal block underneath which a special thermometer is so adjusted that it registers the

[10] Maquenne type metal block; Arthur H. Thomas, Philadelphia, Pa.; Fisher Scientific Co., Pittsburgh, Pa.

temperature of the center area. The top of the block is polished by means of sandpaper and a small amount of the finely powdered compound is sprinkled on the center of the block as the temperature is raised either by means of a flame beneath the block or electrically by means of resistance wire. If the compound does not melt immediately when it is dropped on the metal surface, it is removed either by brushing off with a fine brush or by means of a filter paper; the temperature is raised and the procedure is repeated until a temperature is reached at which the fine crystals melt immediately upon coming in contact with the metallic surface.

Silicone fluids for heating baths. A number of liquids that have excellent properties as fluids for heating baths have been made commercially available in the past few years.[11] These liquids, obtained by the polymerization of the organosilicon compounds, are colorless, clear, stable to heat and resistant to most chemical reagents; in addition, they exhibit a low rate of viscosity change over a wide temperature range and have higher flash points than petroleum oils of equivalent viscosity. For temperatures up to 350° fluid Type 550 of 75 centistokes viscosity has been found useful by the authors. It can be used without discoloration or change for a year or more; rubber or metal bands immersed in the liquid even at high temperatures remain unattacked. The fluid is occasionally filtered through cotton or glass wool. The cost of the fluids (about $1.40 per 100 ml) may be considered by some as a disadvantage to their widespread use for this purpose.

Procedure for liquid-bath apparatus. If the beaker or the flask apparatus is used, the bath is filled three-fourths full with the liquid. The thermometer is so adjusted that the rubber band holding the capillary tube is out of the bath, and the mercury bulb is near the middle of the oil bath. The beaker is heated over an asbestos wire gauze. The flask or the Thiele apparatus is heated by a small free flame. In the Thiele apparatus the oil level is about 10–15 mm above the circular side tube and the thermometer 15 mm below it, so that the latter is near the midpoint between the upper and lower side arms.

When the thermometer bearing the capillary tube has been adjusted, the beaker or flask is heated rapidly to about 10–15° below the known melting point of the substance. If the substance is an unknown, the approximate melting point is first determined by heating fairly rapidly until the substance has melted. The bath is then allowed to cool to

[11] Dow Corning Corporation, Midland, Michigan; also carried by Wilkens-Anderson Co., Chicago, Ill.

about 20° below the observed melting point; the thermometer is carefully removed and held until it has acquired the temperature of the room; and then a new loaded capillary tube inserted. The thermometer is replaced and the bath heated until the temperature rises to within 10–15° of the melting point. The flame is removed until the temperature begins to drop. The heating is then resumed at such a rate that the temperature rises 2–3° per minute, the liquid bath being stirred so that the temperature in the various parts of the apparatus will be as uniform as possible. When the temperature comes to within 2–4° of the melting point, a rise of 1° per minute is desirable. The temperature at which the substance begins to liquefy and the temperature at which the liquid is clear are noted. The interval of temperature is recorded as the melting-point range of the substance. If the compound melts without decomposition, it is suggested that a second and a third observation be made by removing the thermometer from the bath, holding it in air until the liquid in the capillary solidifies, then repeating the melting-point determination.

Thermometer correction. The temperature that is read on the thermometric scale must be corrected because there are several errors in such determinations. One source of error arises from the construction and calibration of the thermometer. The bore of the capillary may not have the same diameter throughout; further, the scale graduation and the calibration of low-priced thermometers are not very accurate. A second source of error is the method used in the common melting-point apparatus. The common thermometer has been calibrated while being totally immersed in a bath. In the melting-point apparatus described, only a part of the stem is immersed. The column of mercury above the liquid in the bath will show a lower temperature than that for which the thermometer was calibrated. Therefore either a thermometer calibrated by partial immersion should be used, or a correction must be made for the unequal heating of the mercury in the stem of the thermometer. The correction for unequal heating of the thermometer is given by the formula: *Stem Correction (degrees)* $= 0.000154\ (t_o - t_s)N$, where the fraction 0.000154 represents the difference in the coefficients of expansion of glass and mercury, t_o is the temperature read, and t_s is the average temperature of the column of mercury not immersed in the substance; t_s is determined (approximately) by reading a second thermometer whose bulb is held at the midpoint of that part of the column of mercury not immersed in the substance. N is the length in degrees of the portion of the column that is not immersed. The error due to this variable is small at temperatures below 100°, but may amount to 3–6° at 200° and above.

The calibration of the thermometer is recommended as the first opera-

tion before any derivatives are prepared. It is essential that the same apparatus and rate of heating be used throughout the calibration and on the melting points of the derivatives. For the calibration of thermometers the following pure substances may be used:

SUBSTANCE	M.P.	SUBSTANCE	M.P.
Water-Ice	0°	Anthracene	216.0°
p-Nitrotoluene	51.9°	*Sym*-Diphenylurea	238°
Naphthalene	80.8°	*p*-Nitrobenzoic acid	241°
Benzoic acid	121.7°	Phenolphthalein	265°
Salicylic acid	159.8°	Anthraquinone	285°

The deviation is plotted as shown in Figure 15. Curves *B* and *C*, which are for the ordinary thermometers in general use, are standardized for total immersion. Curve *A* is for a thermometer costing about the same as *B* and *C*, but standardized for 76-mm stem immersion. Inspection of the curves indicates that the magnitude of the correction to be applied is much smaller for the 76-mm stem immersion thermometer than for the total immersion thermometers. The correction to be applied as deter-

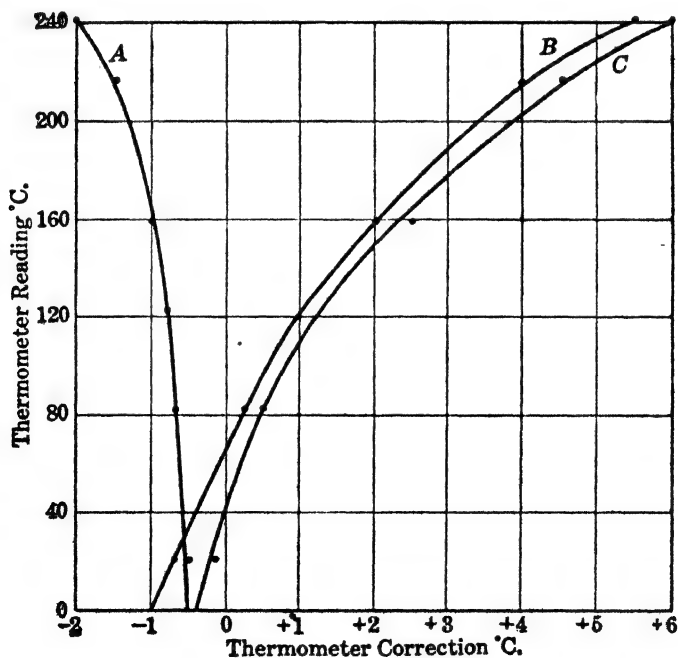



FIGURE 15

Calibration Curves of Three Common Thermometers

mined by the melting point of known pure substances agrees fairly closely with those calculated by means of the above formula. The thermometer *C*, according to the determination of the melting point of *p*-nitrobenzoic acid, requires a correction of +6.0°; according to the calculation from the formula the corrections on two determinations were 5.92° and 5.76°. Since there is no great differential in the price of the thermometers calibrated by partial immersion, they are recommended for the use of beginners with the provision that they should be calibrated. Such thermometers are marked with an etched ring at the 76-mm mark and above it bear the inscription, "76-mm immersion." To use such thermometers the stem is immersed so that the mark is even with the surface of the liquid bath. These thermometers are recommended in place of the common thermometers.

Precision melting-point apparatus. Extensive investigations have shown that discrepancies occur in the values of melting points taken with

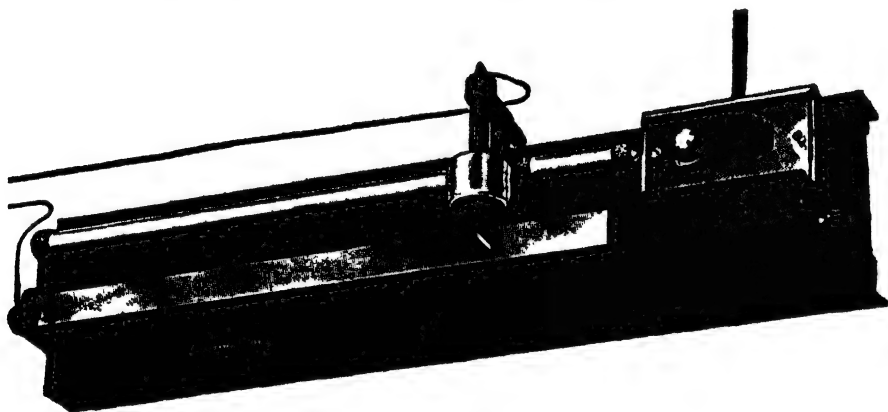



FIGURE 16

Dennis Melting-Point Apparatus

(Parr Instrument Co.)

different types of melting-point apparatus. Unstirred baths give higher values; high-speed, mechanically stirred oil baths give low values; and the hand-stirred devices afford intermediate values. For the accurate work required in research, precision apparatus must be used. The Markley apparatus[12] uses a modified Thiele tube to permit high-speed stirring by means of a turbine-pump assembly that insures uniform heat interchange. The Hershberg apparatus[13] consists of a modified Thiele

[12] Markley, *Ind. Eng. Chem., Anal. Ed.*, 6, 475 (1934).
[13] Hershberg, *ibid.*, 8, 313 (1936).

apparatus electrically heated and of such length as to permit total immersion of the thermometer stem. Both apparatus are excellent for research work or where great accuracy is desired, but they are too elaborate for beginners.

Figure 16 shows the Dennis[14,15] melting-point apparatus. It consists of a silver-plated copper bar electrically heated at one end; the temperature at the top surface of the copper bar is determined by a sliding and traveling arm that carries a chisel-shaped contact of constantan wire. When the constantan touches the heated copper bar, a thermocouple is developed at the point of contact of the two dissimilar metals; this creates an e.m.f. that is proportional to the temperature at the point of contact. By means of a potentiometer, the e.m.f. generated by the thermocouple is measured, and in this manner the temperature of the bar at the point of contact is calculated. For determination of the melting point of a substance, a few particles of the finely powdered material are dropped on the heated bar in order to locate a region where the temperature is high enough to melt the sample; a narrow train of powder is then sprinkled in this region, and the constantan pointer is moved on the bar until the line of molten material coincides with the position of the constantan pointer.

The accuracy of the determination depends upon the sensitivity and accuracy of the potentiometer that is used to measure the e.m.f. generated by the thermocouple. The apparatus is not supplied with a potentiometer, and the choice of the particular type is left to the user. A direct-reading portable potentiometer with an accuracy of 1° is commercially available.[16] For more precise measurements an accuracy of 0.2° is claimed by the use of more sensitive potentiometers.[17] The maximum temperature that can be reached at the hottest point on the bar is 210°, and therefore the apparatus is limited to determinations of melting points at temperatures under 200°.

Figure 17 shows the Koffler micro melting-point apparatus;[18] it consists of an insulated stage (A) 90 mm in diameter and 20 mm high, heated by an embedded Nichrome unit. The sample, which may consist of a single crystal, is placed on a short slide situated within the heating chamber and covered with a micro cover glass. A glass baffle fits over the mounted sample; a special thermometer is inserted into an opening directly under the heating chamber. Each thermometer is calibrated by

[14] Dennis and Shelton, *J. Am. Chem. Soc.*, **52**, 3128 (1930).

[15] Parr Instrument Co., Moline, Ill. Model MP-11.

[16] Wheelco Instrument Co., Chicago, Ill. Apparatus No. 312. Leeds and Northrup, Philadelphia, Pa. Apparatus No. 8658.

[17] Leeds and Northrup. Apparatus No. 8662 or K-2.

[18] Arthur H. Thomas Co., Philadelphia, Pa. Apparatus No. 6886-A.

the manufacturer in terms of melting points of sharply melting substances for the particular stage in which it is used. This procedure eliminates thermometer corrections and permits the direct determination of corrected melting points. The heating of the stage is controlled by a special rheostat designed to give reproducible settings. The stage is inserted in the observation platform of a microscope; when the temperature reaches the range at which the substance melts, the smaller crystals and

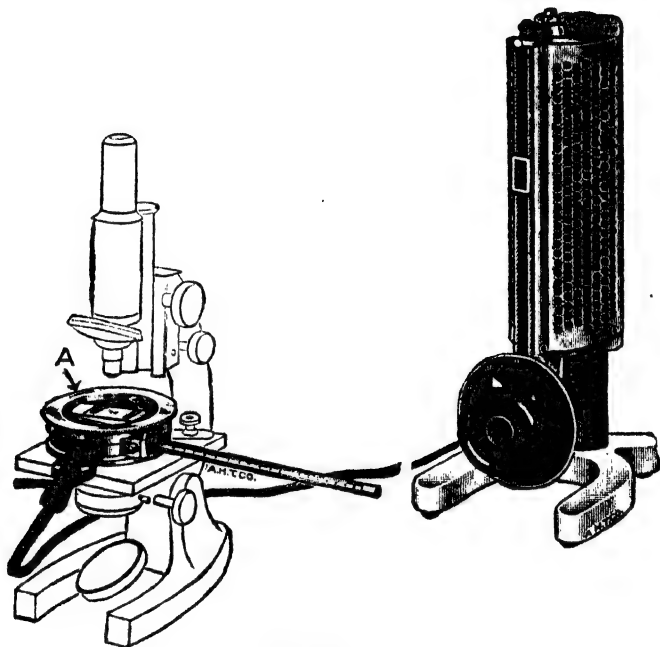



FIGURE 17

Koffler Micro Melting-Point Apparatus

(Arthur H. Thomas Co.)

particles viewed through the microscope coalesce into round droplets with remnants of the solid phase embedded in the liquid. The observed temperature at the time this equilibrium point is reached is the melting point of the substance.

The micro hot-stage apparatus offers a number of advantages. It permits the determination of melting points with samples as small as a single crystal; it may be used for determinations up to 350°C with greater accuracy and far less hazard from accidents than with the liquid-bath apparatus. The accuracy for temperatures up to 200° is $\pm 0.5°$ and for higher temperatures, $\pm 1.0°$.

Determination of melting points of substances or mixtures that melt between −50° and +40°. This method is useful for the determination of melting points of substances or eutectic mixtures that are liquid at ordinary temperatures. Although the occasion for using this method does not often arise, it is convenient with compounds that boil with decomposition or have high boiling points, but melt above −50°.

Apparatus used in the determination is shown in Figure 18. It consists of an 8-inch tube with a side arm; the closed end of the tube is blown to a bulb of 35–40 mm in diameter. The commercial model has a small glass tube reaching from the side arm to the bottom of the tube, curving upward and ending in an orifice of about 0.3–0.5 mm for blowing a stream of bubbles. The same purpose may be accomplished by inserting through the top of the apparatus a 4-mm tube drawn to a capillary at the end and bent at a right angle at the top. A 3-mm rubber tube is connected to the tube and held at the mouth for blowing a stream of bubbles. A toluene or alcohol-filled thermometer graduated from −50° to +50° is inserted through a cork, which is held by a clamp so that the end of the thermometer bulb reaches 10 mm from the bottom. About 25–30 ml of methanol are added to the bulb to serve as bath liquid.

FIGURE 18

Apparatus for Determination of Melting Points of Substances That Melt between −50° and +40°

A capillary tube 1 mm in outer diameter and 70–80 mm in length is sealed at one end to serve as a melting-point tube. Another capillary tube is prepared, open at both ends, with an outer diameter of 0.2–0.4 mm and length of 110–120 mm. The smaller capillary tube should be inserted in the melting-point tube so that one end reaches the bottom freely. A small droplet of the liquid (1 mg or less) is placed on a small watch glass. While the melting-point tube is held with one hand, the smaller capillary is removed and placed vertically, so that one end of the open capillary is immersed in the liquid, which by capillary attraction rises rapidly into the tube to a height of 40–50 mm, depending on the diameter of the capillary and the properties of the liquid. The smaller capillary is inserted into the melting-point tube and pushed gently down until the end reaches the bottom. While being pressed gently downward, the small capillary is rotated so that the liquid descends and fills the melting-point tube to a height of 3–4 mm. Thereupon the capillary is rapidly withdrawn, with the result that the sides of the melting-point

tube become streaked with the liquid. The clean end of the smaller capillary is held momentarily in the flame so that the open end is just sealed off, forming a very small bead at the end. The sealed end of the capillary is inserted into the melting-point tube to be used as a stirring rod for the crystallization.

If the melting point of the solid is above −15°, an intimate mixture of ice and salt is placed in a 50- or 100-ml beaker, and the melting-point tube is immersed and allowed to remain for 3–5 minutes. When the liquid has crystallized, the melting-point tube is removed and the lower end is held momentarily between two fingers so as partially to melt the crystals. The melting-point tube is replaced in the ice-salt bath, and the mixture of crystals and liquid is stirred by raising the capillary rod upward and moving it downward until the mass begins to solidify; then the capillary rod is withdrawn. Thus the lower end of the melting-point tube contains a crystalline mass, while the sides are covered with a film of crystals to a height of 10–20 mm, which gives the melting point tube a foggy appearance. When the tube is heated, this foggy film of crystals vanishes suddenly, thereby furnishing a better criterion of the temperature at which melting takes place.

If the liquid does not crystallize, because of supercooling, it is rubbed against the walls of the vessel by means of the capillary stirring rod. Some substances require considerable agitation before they begin to crystallize. Seeding may be used to induce crystallization. The watch glass on which the droplet was placed for transfer to the capillary is chilled by placing it on the freezing mixture and rubbing it with a spatula. As soon as the crystals have formed, the capillary rod is withdrawn from the tube, and the bead at its end is made to touch a few minute crystals and then rapidly transferred back to the melting-point tube. If the melting point of the substance is between −18° and −50°, the bath used is a mixture of dry ice and acetone or methanol. About 75 ml of the acetone or alcohol are placed in a 250-ml beaker wrapped in a towel, and then small pieces of dry ice are added until the required temperature has been reached.

While the melting-point tube is being prepared, the bulb of the melting-point apparatus is immersed in a cooling mixture similar to that used for chilling the melting-point tube. A 250-ml beaker is used; the bulb, with the thermometer resting on the bottom, is immersed in the cooling mixture and stirred occasionally with the thermometer. When the temperature has fallen about 10° below the melting point of the compound placed in the capillary tube, the thermometer is rapidly transferred close to the melting-point tube; the latter is attached by means of a rubber

band to the thermometer. The melting-point apparatus is removed from the cooling bath and clamped in position on the stand; the thermometer is removed from the cooling bath and lightly shaken to remove adhering liquid and rapidly adjusted in place within the liquid bath of the melting-point apparatus. The bulb is wiped off with a dry cloth and the melting-point tube inspected. If the operations have been made with proper care, the temperature will be several degrees below the melting point, and any solid that may have melted during the adjustments will have solidified. The bath is heated by holding the small rubber tube between the lips and blowing a stream of bubbles intermittently through the liquid. The temperature rises about 1° for every one or two minutes. If more rapid heating is required, as when the temperature is much below the melting point, the bulb is warmed by holding it in the hand for a few seconds or by applying momentarily the smallest flame of a microburner. When the foggy film above the mass of crystals in the melting-point tube vanishes, further heating or blowing bubbles through the bath is discontinued and the temperature noted. If the compound is pure, the crystals melt within 0.5° of this temperature. If the crystals are impure, the mass of crystals may not completely melt until the temperature has been raised several degrees above this point.

Melting points of substances that decompose. A number of organic compounds, such as the amino acids and the osazones from sugars, melt with decomposition. As the sample is heated in the melting-point tube, decomposition begins before it has reached the melting temperature; the presence of the decomposition products will produce a lowering of the melting point of the substance. The extent of the lowering depends on the length of time the sample has been heated at the decomposition temperature; therefore the extent of the melting point depression depends on the rate of heating. For example, pure phenyl-*D*-glucosazone melts at 209–210° when the liquid bath is heated at such a rate that the temperature rises 40–60° per minute; the same substance melts below 200° if the rate of temperature rise is 8–10° per minute. Therefore if the substance shows decomposition near the melting temperature it is advisable to redetermine the melting point several times, heating the bath so that the rise of temperature is about 60° per minute. Another method is to preheat the bath to about 5° below the temperature noted in the first determination and then to immerse the thermometer to which the capillary is attached and heat rapidly.

Mixed melting points. It is a common practice in the identification of organic substances to use the method of mixed melting points. To

illustrate the method, let it be assumed that an organic liquid under investigation boiling at 106–108° is provisionally identified as isobutyl alcohol. One of the derivatives prepared for the final proof of the identity is the 3,5-dinitrobenzoate; the melting points of the crystals of this derivative were 84–85° after the first crystallization and 85–86° for the second crystallization. The melting point of the 3,5-dinitrobenzoate of isobutyl alcohol is listed in Table 5 (page 370) as 87°. For a mixed melting point the 3,5-dinitrobenzoate of a known sample (100–200 mg) of isobutyl alcohol is prepared, and the melting point of the crystals is determined. Approximately equal amounts of the crystals of the dinitrobenzoate derived from the "known" and the "unknown" samples are thoroughly mixed by crushing in a mortar or a watch glass and the melting point of the mixture is determined. If all three melting points are essentially the same, or if the melting point of the mixture lies between that of the two dinitrobenzoates, the "unknown" is identified as isobutyl alcohol. If the unknown is not isobutyl alcohol, the melting point of the mixture of the two dinitrobenzoates will be at least 10° or more below that of the components and the melting will not be "sharp" but over a range of several degrees.

The basis of the above method is that a mixture of two unlike crystalline substances will melt considerably lower than either of the individual components alone, owing to the formation of a eutectic. It should be remembered, however, that there are cases of unlike crystalline substances that show a higher melting point than either of the two components because of the formation of a new compound. In a number of instances two different compounds melting a few degrees apart may show no depression in melting point when mixed.[19] For example, naphthalene picrate, m.p., 151°, and thionaphthalene picrate, m.p., 149°, melt, when mixed, at 149°.

From the above considerations it is obvious that failure to observe a lowered melting point in a mixture of two derivatives prepared from a known and an unknown is not a reliable proof of identity unless all other data—solubility tests, functional group tests, and physical constants—are in agreement. With this reservation, the practice of taking mixed melting points, using samples of derivatives from the unknown and the compound tentatively identified as the unknown, may be resorted to whenever two successive crystallizations fail to produce a rise of more than 2° in the melting point of the derivative.

[19] Lock and Nottes, *Ber.*, **68**, 1200 (1935); Gibby and Waters, *J. Chem. Soc.*, **1931**, 2151.

Distillation

Simple distillation. Simple distillation is used for the purification of an organic compound that is liquid at room temperature if the impurity is not volatile or if the impurity is volatile but present in small amounts and boils considerably below or above the boiling point of the compound. For simple distillation the boiling point of the compound should be below 250° and the compound should not decompose when boiled at normal atmospheric pressure.

Three arrangements of commercially available apparatus for simple semimicro distillation are shown in Figures 19, 20, and 21. Figure 19 is

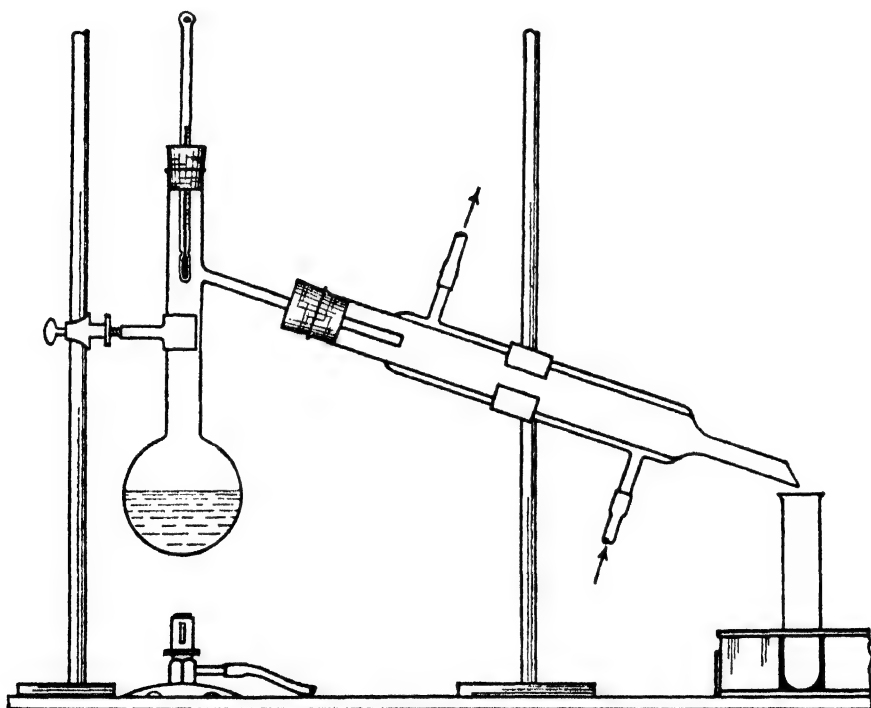



FIGURE 19

Traditional Set-up for Distillation

the traditional setup with use of small vessels. The distilling flask has a capacity of 10 or 25 ml and the condenser a length of 160 mm. The apparatus shown in Figure 20 is a more convenient arrangement. The distillation tube is an ordinary 6-inch (20 x 150 mm) or 8-inch (25 x 200 mm) tube with a side arm.[20] The distilling tube is fitted with a cork

[20] Wilkens-Anderson Co., Chicago, Ill. Apparatus No. 5824-DT and 3672-B.

holding the thermometer; the latter is so adjusted that it is 5 mm below the side-arm opening. The side arm is connected by a small piece of rubber tubing (3–4 mm) to the delivery tube, which has a diameter of 4 mm. Both the delivery tube and the condenser should be fitted

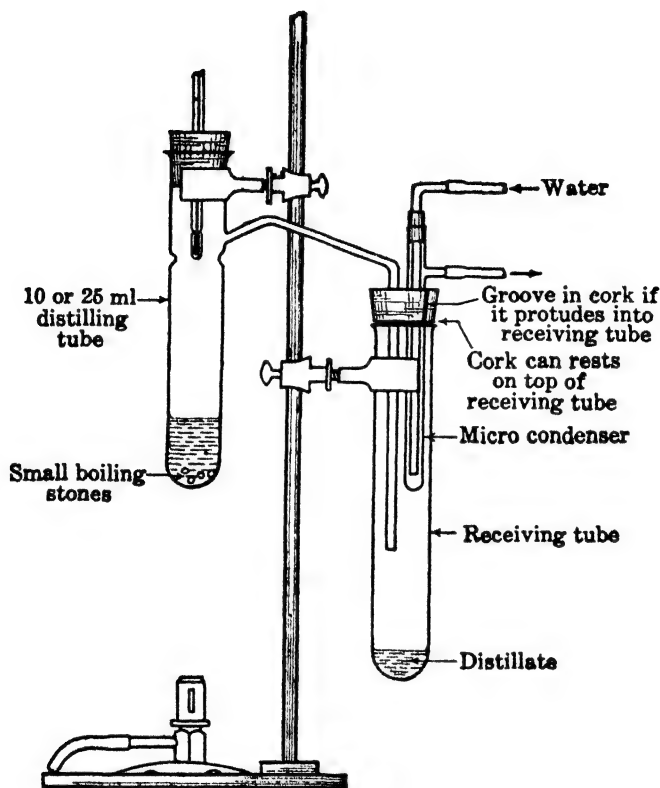



FIGURE 20

Semimicro Apparatus for Distillation

through a cork into an ordinary 6-inch test tube, which acts as a receiver. The opening for the condenser is larger than the diameter of the condenser tube, so that it fits loosely; it is held in place by inserting a match or small stick, and thus the system is not closed. A test tube of any size may serve as a receiver, provided its diameter is sufficient to hold the delivery tube and the condenser. The cork need not fit into the receiving tube but may be adjusted to rest on top of its mouth. Another method of keeping the system open is to cut a groove on the side of the cork as shown in the diagram. In such a case the cork may be inserted into the receiving tube.

The liquid to be distilled is placed in the distilling tube, and two small boiling stones about the size of grape seeds are added. All connections are inspected, and the receiving tube is so adjusted that the condenser and the delivery tube reach to about two thirds of the depth of the tube. Heat is applied with a microburner, the flame being moved to and fro. As the liquid begins to boil, the vapor condenses on the sides of the distilling tube and returns to the boiling liquid. The flame is adjusted so that the vapors ascend very slowly and reach the thermometer bulb at least one minute before they pass through the side tube. In this manner the thermometer is heated to the temperature of the vapor. The vapor passes into the receiving tube, condenses on the micro condenser, and runs to the bottom of the tube. Thus the progress of distillation is determined by the amount of liquid in the receiving tube.

FIGURE 21A
Semimicro Apparatus for Distillation Using Pear-shaped Tube

The temperature at which the liquid appears in the receiving tube is recorded. The distillation is continued slowly until the mercury column in the thermometer remains nearly stationary, when the flame is removed and the receiving tube is changed. Heating is then resumed, and, as soon as distillation begins, the flame is adjusted so that the liquid in the receiving tube increases slowly. A little experience is necessary before the technique is mastered. Toward the end the flame, manipulated by hand, is moved to and fro in order to avoid superheating. When a minute amount of liquid is left in the distilling tube, the distillation is discontinued and the apparatus is disconnected and cleaned. It will be found advisable to allow the cork to remain in place on the delivery tube and condenser. The delivery tube and condenser are cleaned by rinsing with a little acetone or denatured alcohol, wiped, and placed in a small cardboard box.

Figure 21*A* shows another semimicro distillation arrangement; it is similar to that shown in Figure 20, but is more convenient when the volume of the liquid to be distilled is less than 5 ml. The distilling tube has an overall length of 100 mm; the length of the pear-shaped bulb is 40 mm, and its diameter at the bulge is 25–27 mm. The capacity of the distilling tube is 10 ml. A pear-shaped distilling tube of 25-ml capacity is also commercially available.[21] Figure 21*B* shows a combination of condenser and receiver for semimicro distillation proposed by Potempa.[22] Cold water circulates in jacket *A*, and the distillate is collected in receiver *B*; a suction pump may be connected at side arm *C* when distillation under reduced pressure is desired.

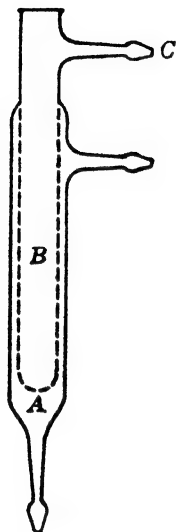



FIGURE 21B
Combination of Condenser and Receiver for Semimicro Distillation (Potempa)

Fractional distillation. Figure 22*A* shows an arrangement of apparatus for semimicro fractional distillation of 5–10 ml of liquid. The fractionating column is 180 mm in length and 8–8.5 mm in outside diameter;[23] the upper end is 20 mm in diameter to permit insertion of the thermometer. Three types of packing are recommended for this column.

The most convenient type of packing is made through *crinkle glass wool;*[23] about 500–600 mg of the glass wool is weighed out and then placed in small amounts into the wide part of the column and lightly forced down into the tube by means of a 4–5 mm glass tube. The packing should be uniformly distributed throughout the length of the column and should not be tightly packed in one part and very loose at another. This type of packing combines efficiency in fractionation together with low cost and ease in filling the column.

A second type of packing is made by winding glass yarn,[23] of 1.3 mm thickness, around a glass rod 4 mm x 160 mm. One end of a piece of glass yarn 400–500 mm long is attached firmly to the end of the glass rod by means of a fine wire or thread. While the glass yarn is held in one hand, the rod is rotated so that 25–30 spirals of yarn are wound around it. This end of the glass yarn is tied to the rod as was the first. The two ends are covered with a small amount of acid-proof cement,[23] which

[21] Wilkens-Anderson Co., Chicago, Ill. Apparatus No. 5824-DT, and 3672-B.
[22] Private communication, S. J. Potempa, Loyola University, Chicago, Ill.
[23] Wilkens-Anderson Co., Chicago, Ill. Column, No. 5824-FC; crinkle glass wool, 5824-W; glass yarn, 5824-Y; cement, 2300-B. The crinkle glass wool should be boiled with water and thoroughly washed before use to remove the compounds used as binders in the manufacture of the fibers.

is allowed to set; one end is made thicker so that it will not go into the column. The spiral should fit neither too tightly nor too loosely within the column and should be capable of being inserted gently without the use of much pressure. The spiral is inserted through the top so that the thicker end just protrudes into the wider chamber. If the upper end is not sufficiently thick and shows a tendency to slip within the narrow column, a piece of thin wire is wound around it to hold it in place.

A third type of packing for efficient semimicro fractionation is the Podbielniak Heli-Grid packing. The column and packing are assembled by the manufacturer and are commercially available.[24] The packing consists of several Nichrome wire coils wound around a central core. The complete setup of flask, column, and vacuum jacket are shown in Figure 22*B*. A distillation curve of a four component mixture is shown in Figure 22*C*.

FIGURE 22A
Apparatus for Semimicro Fractionation

For insulation an asbestos or a glass vacuum jacket is used. The asbestos is 4–5 mm long and 100–110 mm thick and is made by winding around an 8-mm tube several thicknesses of asbestos paper, which have been painted with a sodium silicate solution and allowed to dry. The vacuum jacket is made of Pyrex glass and contains several metal radiation shields spaced within the evacuated section in which the pressure is about 1×10^{-5} mm. Both jackets are available.[25] One end of the column is inserted through a cork and placed in the mouth of a 10- or 25-

[24] Podbielniak Centrifugal Super-Contactor Company, Chicago; Podbielniak, *Ind. Eng. Chem.*, **13**, 639 (1941).
[25] Wilkens-Anderson Co., Chicago, Ill.

ml round-bottom flask or a test tube. The side arm of the column is connected to the condensing-receiving system as described in the section on simple distillation.

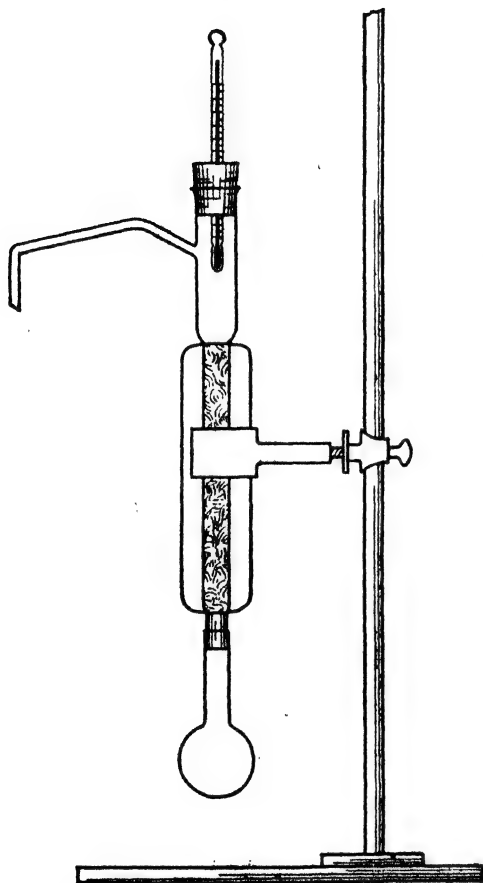



FIGURE 22B
Podbielniak Microcolumn with Vacuum Jacket

The most important factors determining the efficiency of fractional distillation are: (a) height of column; (b) nature of packing· (c) insulation; and (d) rate of distillation. Even with a column so designed as to meet the first three factors, the efficiency of the fractionation rapidly diminishes if the withdrawal of distillate is at the rate of more than 0.3 ml per minute. It is advisable to wet the column first with some of the mixture to be fractionated; this is best accomplished by adding the liquid to be distilled slowly through the top of the column into the boiling vessel, from which the cork has been loosened to permit the escape of air. The various connections are inspected and adjusted, and heat is slowly applied to the boiling vessel with a small flame. In the beginning there will be a certain amount of refluxing within the column; when flooding appears on the top of the column, the flame is removed and the vessel is allowed to cool momentarily. Heating is resumed with the flame moved to and fro until the vapor begins to enter the side tube. The heating is then adjusted so that the rate of distillate withdrawal is 0.2–0.3 ml per minute. The receiving tubes may be calibrated at the 0.5-, 1-, 2-, and 5-ml marks with thin strips of gum paper. If care is used, 5–10 ml of mixtures may be separated efficiently with a single fractionation.

In Figure 23 is shown a type of apparatus for the fractionation of 1–2 ml of liquid. The column is of similar construction to that described,

except that the top is not flared for the insertion of a cork to hold the thermometer. The latter is fitted through a short piece of rubber tubing and then fitted snugly within the upper part of the column. Two types of microflasks may be used to fit the column. One type has a ground joint as shown in Figure 23; the other has a longer neck and is connected with the column by means of rubber tubing.

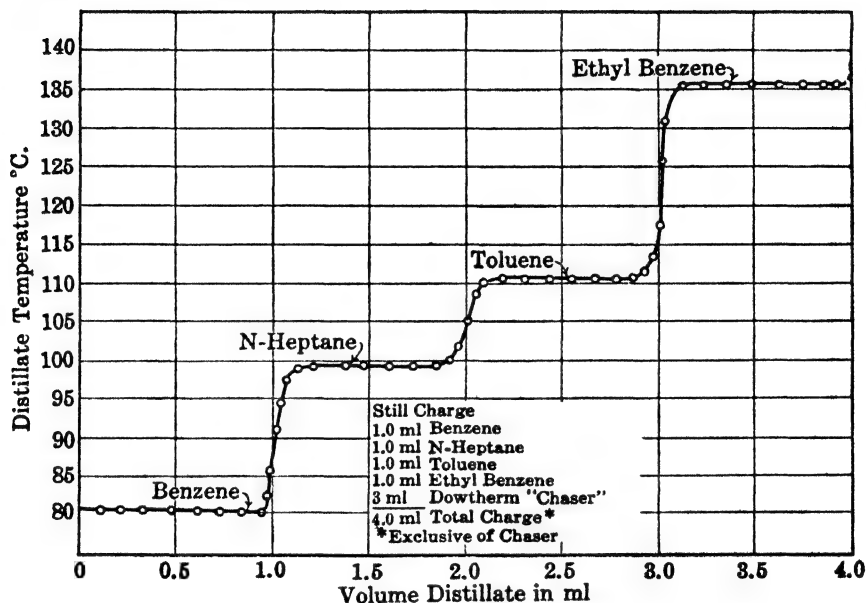



FIGURE 22C

Distillation Curve of a Four-component Synthetic Mixture, Using a Podbielniak Microcolumn

Fractionation of a few drops of liquid may be effected by using the apparatus shown in Figures 24 and 25. In the Emich microfractionation tube[26] shown in Figure 24, the distillate collects in the bent part of the side arm *D* and is removed by means of a capillary pipette. The apparatus shown in Figure 25 is constructed from a piece of glass tubing that is 10 mm in diameter. A piece about 90 mm in length is selected and sealed at one end. The lower end is filled with crinkle glass packing (page 44) to a height of 20–30 mm. A special microcondenser with a well at the lower end is fitted at the upper part of the tube. An ordinary microcondenser jacket is heated at the lower part in a hot pointed flame until the glass is soft, and pushed inward and downward by means of the

[26] Arthur H. Thomas Co., Philadelphia, Pa.

pointed end of a deflagrating spoon. The well holds 1–2 drops of liquid. This type of microcondenser jacket is commercially available.[27]

Two or three drops of the liquid to be fractionated are added on top of the glass packing, and the special microcondenser is inserted. The tube is heated by means of a very small flame from the microburner until the vapors of the liquid begin to condense on the sides of the tube just above the glass fibers. The flame is then adjusted so that the liquid collects in

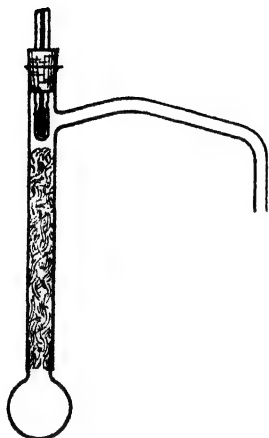



FIGURE 23
Apparatus for Fractionation of 1 to 2 ml of Liquid

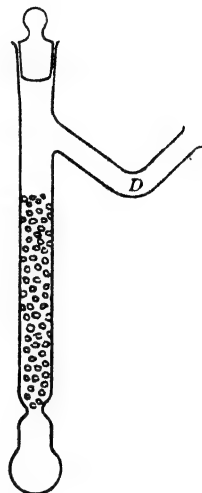
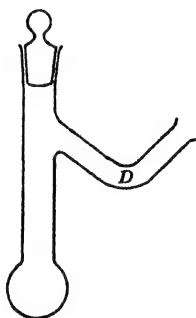



FIGURE 24
Emich Microfractionation Tubes

the well at such rate that it takes about five minutes for it to fill. The distillate is removed by lifting the condenser and inserting a capillary pipette in the well. In this manner 5–10 fractions may be collected from the fractionation of a few drops.

Semimicro steam distillation. Two different setups may be used, depending upon whether or not the heating bath shown in Figures 26 and 52 is available. If this heating bath is not available and the amount of liquid to be distilled is about 5–7 ml, the apparatus shown in Figure 26 is used. A solid No. 9 rubber stopper or a No. 20 cork is fitted onto a wide-mouth 250-ml Erlenmeyer flask. The mouth of this flask has a diameter of about 40 mm. On one side of the stopper an opening for a 6-inch test tube is carefully drilled. Then, on the other side of the stopper, two openings for 4-mm tubing are drilled. The 6-inch tube is inserted in the stopper so that only 20 mm projects outside. A two-hole stopper is placed on the test tube and holds two glass tubes of 4-mm bore. One

[27] Wilkens-Anderson Co., Chicago, Ill. Apparatus No. 3672-D.

tube is 160–170 mm in length and serves as the steam inlet; it reaches almost to the bottom of the tube and is curved at the other end so that it can connect with the steam outlet from the flask. The other is a regular L-shaped short tube to serve as a vapor outlet to the condenser.

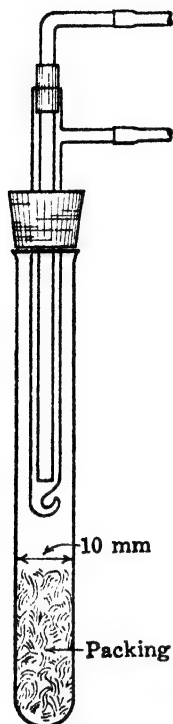



FIGURE 25
Apparatus for Fractionation of a Few Drops of Liquid

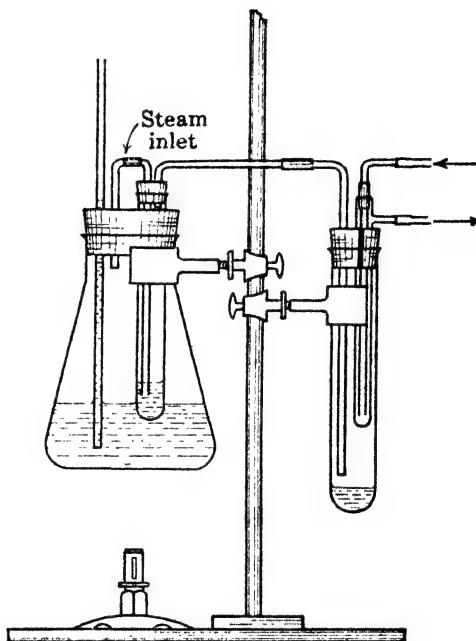



FIGURE 26
Semimicro Apparatus (with a 6-inch tube) for Steam Distillation

About 100–125 ml of water and a few boiling stones are placed in the Erlenmeyer flask. The stopper carrying the test tube fits securely into the mouth of the flask. A piece of glass tubing 300–350 mm in length is fitted through one of the small openings of the stopper and pushed down until one end reaches almost to the bottom of the Erlenmeyer flask. Through the other opening is fitted a glass tube which is so bent that it is aligned with the steam-injecting tube. The connection is made with a short piece of rubber tubing. Perfect alignment of the steam outlet and steam injector is necessary to prevent kinking in the rubber connection. Finally, the vapor outlet from the 6-inch boiling tube is connected to a

regular semimicro condensing system. The apparatus is now ready for charging.

The metal heating bath permits the steam distillation of 15–20 ml of a liquid mixture and also affords great flexibility in operation, for the space to fit the various tubes is not limited. Since the time required for semimicro steam distillation is not long, volumes of 30–40 ml can be steam-distilled in 2–3 portions. To convert the heating bath into a steam-distillation apparatus such as is shown in Figure 27, a No. 20 cork or a No. 9 rubber stopper is fitted into the largest opening of the bath. The stopper is carefully bored to hold an 8-inch tube snugly. The tube is pushed gently in, far enough so that when the stopper is in place the tube reaches almost to the bottom of the bath. A No. 14 cork or No. 6 one-hole rubber stopper is fitted through the other large opening of the bath. A piece of glass tubing, 4–5 mm in diameter and curved slightly at one end, is inserted through this stopper to serve as the steam outlet. It connects through a small piece of rubber tubing with the steam injector, which is a glass tube of the same bore, 210–220 mm in length, and reaches almost to the bottom of the 8-inch tube. The vapor outlet projects 40 mm above the tube before it bends to connect with the condensing system. It is advisable to make the vapor outlet of tubing 5–6 mm in bore, thus minimizing the danger of clogging and of carrying over into the distillate material spattered from the boiling tube. A glass tube 4–5 mm in bore and 300–350 mm in length is inserted through a stopper and placed in one of the small openings of the bath. The long glass tube reaches almost to the bottom of the bath and serves as a water and pressure gauge. The remaining opening of the bath is closed by a solid stopper.

FIGURE 27

Semimicro Apparatus (with an 8-inch tube) for Steam Distillation

The liquid to be steam-distilled is placed in the tube (of either apparatus), and the rubber tubing that joins the steam inlet and steam injector is disconnected. The flask or bath is placed on a ring stand and clamped securely. Heat is applied until the water rises in the gauge and steam issues from the steam-outlet tube. The flame is then removed

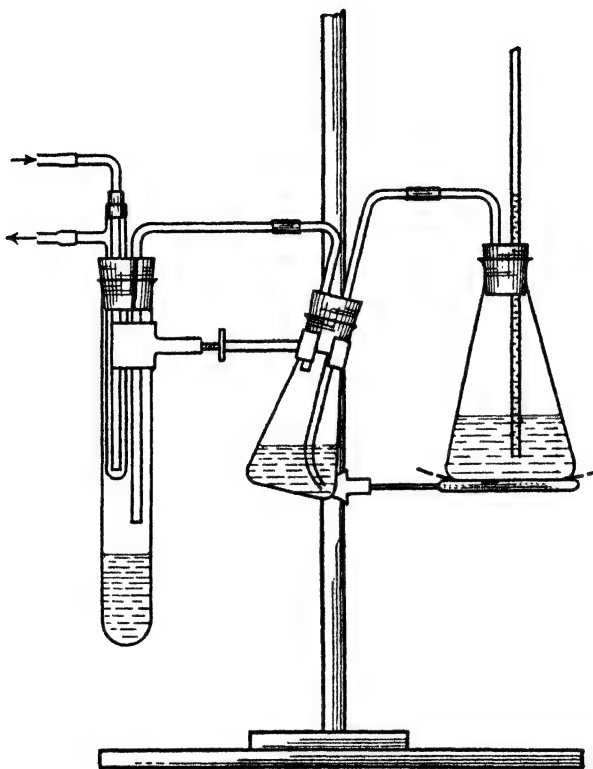



FIGURE 28

Semimicro Apparatus (with small Erlenmeyer flasks) for Steam Distillation

momentarily, and, after about 30 seconds, the steam inlet is adjusted to the injector and heating is resumed. The flame is so adjusted that the splashing does not reach the middle part of the vapor-outlet tube. An 8-inch tube is used in the receiving system, and, if the micro condenser is not sufficient to cool the vapor, a beaker of cold water is raised so as to surround the lower part of the receiving tube.

With a little practice steam distillations may be performed rapidly by use of the apparatus just described. The only difficulty that may be encountered is with foaming liquids, particularly when finely divided solids

are contained in the mixture to be distilled. In such cases the volume of liquid to be steam distilled should not exceed 5–7 ml. If foaming becomes troublesome, the upper part of the boiling tube, near the steam outlet, may be heated by a small flame.

Figure 28 shows an arrangement for semimicro distillation with the use of 2 small Erlenmeyer flasks. This arrangement is useful with mixtures

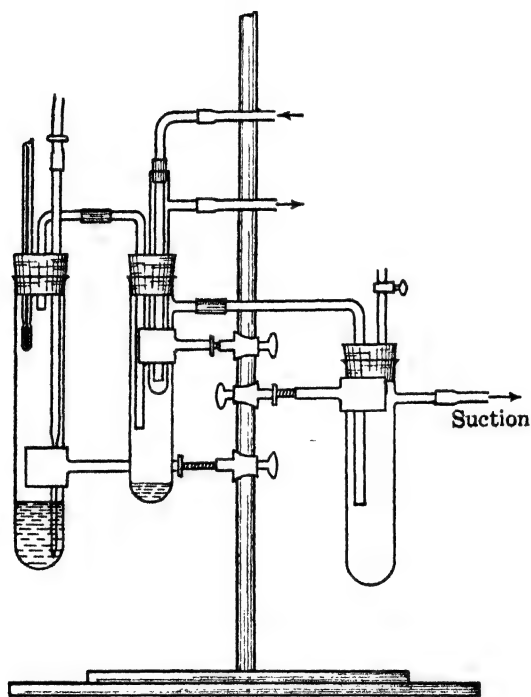



FIGURE 29

Semimicro Apparatus (with an 8-inch tube) for Distillation under Reduced Pressure

that froth badly with steam injection. The apparatus may be used in place of those shown in Figures 26 and 27.

Semimicro distillation under reduced pressure. In semimicro work distillation under reduced pressure is indicated when the compound under investigation: (a) undergoes pyrolytic changes, oxidation, or rearrangement when distilled at atmospheric pressure; (b) has a boiling point much above 200°; (c) has a boiling point below 200°, but the quantity of material available is small.

Two types of apparatus designed for distillation under reduced pressure are described. One is primarily for the college or industrial laboratory

engaged in preparative or identification problems; such apparatus may be set up from easily available and inexpensive equipment. The other type of apparatus is designed to meet the needs of the research laboratory and involves relatively expensive equipment of special construction.

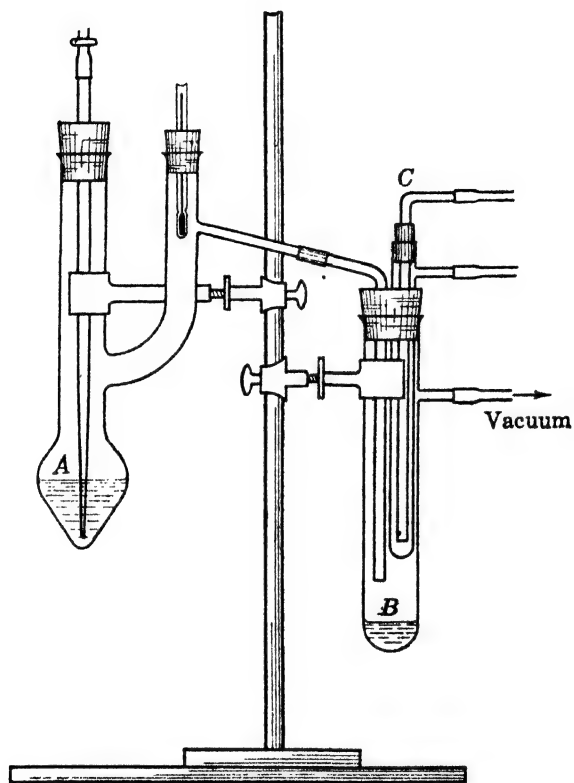



FIGURE 30A

Semimicro Apparatus (with Claisen tube) for Distillation under Reduced Pressure

A = 25- or 10-ml Claisen pear-shaped tube with 110–140 mm side-arm; *B* = 8-inch tube; *C* = microcondenser.

Three arrangements of apparatus for ordinary work in semimicro distillation under reduced pressure are shown in Figures 29, 30*A*, and 30*B*. In Figure 29 two 8-inch test tubes are used. The first tube has a three-hole stopper for the thermometer, a glass tube for outlet of vapor, and a capillary tube. The capillary tube is made of 3–4 mm glass tubing; a piece 100–125 mm in length is sealed to the end of a small piece of scrap tubing. The region near the seal is heated over the flame, the tube be-

ing held at an angle of 75°. When the glass walls of the tube collapse and the inner diameter becomes small, the flame is increased to render the thick-wall section soft. The tube is removed from the flame and pulled out slowly into a capillary. The glass tube for the vapor outlet is

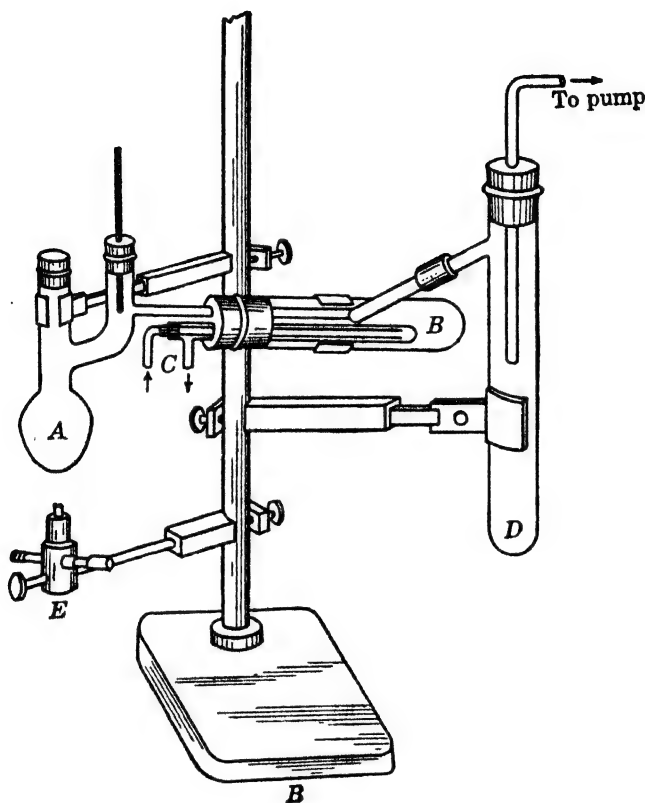



FIGURE 30B

Semimicro Apparatus (with Claisen tube) for Distillation under Reduced Pressure

A = 25- or 10-ml Claisen pear-shaped tube with 110–140 mm side-arm; *B* = 8-inch tube; *C* = microcondenser; *D* = 8-inch tube to serve as trap; *E* = microburner.

4–5 mm in diameter and is bent as shown in the diagram. It can be cut midway between the two tubes and the connection made through thick-wall pressure tubing. The receiver is an 8-inch Pyrex tube with a side arm. It has a two-hole stopper: one connects with the distilling tube and the other holds the microcondenser. The receiver is connected through thick-wall rubber tubing with an 8-inch tube; this serves as a

trap and connects with the manometer and suction pump, and also holds the tube with a stopcock for release of pressure.

There are some drawbacks to this type of apparatus. One is the danger of splashing and bumping, which, however, can be controlled if the volume of liquid to be distilled is not more than 5 ml. Another difficulty is encountered in fitting the thermometer, the outlet tube, and the capillary tube through a No. 5 rubber stopper, but this also can be overcome with a little care and patience. Both of these difficulties are avoided if a 6-inch or 8-inch pear-shaped tube with the Claisen side neck is used. The apparatus shown in Figures 30*A* and 30*B* have 8-inch tubes with a side arm for receiver and trap. The receiver may be made shorter (about 100–120 mm) and shaped as a cone, if the quantity of liquid to be distilled is small. The amount of liquid that can be distilled in such apparatus is 2–15 ml depending on the size of the Claisen tube used. The apparatus is assembled and is then tested by evacuation. *Goggles should be worn at all times.* For a heating bath a small amount of oil is placed in a 150-ml beaker or a small tin can. The beaker offers the advantage of visibility, but the disadvantage of possible breakage.

The liquid to be distilled is placed in the boiling tube by removing the stopper holding the capillary. The stopper is replaced and a small oil bath is raised to the boiling tube. The air inlet is adjusted so that fine bubbles can be counted. Heat is applied under the bath until the first sign of distillate appears, whereupon the flame is removed from under the bath. The temperature and pressure are noted, and heating is resumed until distillation begins and the temperature remains constant, with little variation in the pressure. The air inlet is closed and the pressure is released slowly. The receiver is changed by loosening the stopper, withdrawing the tube, and replacing it with a dry, clean tube immediately. If this precaution is not observed, moisture will condense on the microcondenser. If the receiver is not replaced at once, the condenser should be wiped off with a clean, dry cloth just before the tube is fitted on the stopper. Evacuation is resumed, the oil bath is raised, and the inflow of air is adjusted. Heat is applied slowly until distillation is resumed. The temperature and pressure are recorded and heating is applied intermittently so that the distillation proceeds evenly. When the temperature begins to rise or the amount of liquid in the boiling tube is very small, the distillation is discontinued.

Figures 31, 32, 33, and 34 represent four of the many types of semimicro apparatus of special construction that have been proposed for distillation under reduced pressure.

Figure 31 shows the Fränkel vacuum microdistilling apparatus.[28] It consists of a distilling flask having a capacity of 10 ml, and a receiving vessel connected with the flask by an interchangeable ground joint. Inside the receiving vessel fit six receiving tubes, which may be brought into position to receive fractions of the distillate through rotation of the receiving vessel by means of the supporting clamp. The receiving tubes are kept in position in the receiver by means of a cylindrical glass spacer. The receiving tubes and the spacer have small holes near the top for handling by a hooked wire or special forceps. A special thermometer with ground joints fits in the neck of the flask.

FIGURE 31
Fränkel Vacuum Microdistilling Apparatus

Figure 32 shows the Bernhauer[28] vacuum microdistilling apparatus. It consists of a small Claisen flask, capacity 10 ml, which has a long side arm. A special jacket 200 mm in length fits over part of the extended side arm and serves as a condenser. The lower part of the side arm fits through a manifold having three outlets for receiving tubes and one for connection to the vacuum pump. Three special receiving tubes fit against the manifold outlets by means of rubber tubing. The distillate may be directed from one receiving tube to another by rotating the manifold slightly.

Figures 33 and 34 show apparatus developed by the authors.[29] The arrangement shown in Figure 33 consists of a special Claisen type of distilling tube that connects through a No. 5 two-hole rubber stopper with a special manifold; a micro-condenser is inserted through the same stopper holding the side arm of the distilling tube. The glass manifold has a side arm in the upper part to connect with the vacuum pump and at the lower end a bulb with multiple outlets. Four outlet tubes 4 mm in diameter connect into the receiving tubes by means of rubber stoppers. The jacket is slightly rotated in order to divert the distillate from one tube to another. This apparatus has been used to distil under reduced

[28] Arthur H. Thomas Co., Philadelphia, Pa.
[29] Wilkens-Anderson Co., Chicago, Ill.

pressure quantities from 0.5 ml–15 ml. Claisen tubes of 5 ml, 10 ml, and 25 ml are available.

Figure 34 shows apparatus designed for micro and semimicro fractionation under reduced pressure. The pear-shaped distilling flask has a column 30–40 mm in length, which may be filled with glass fibers when

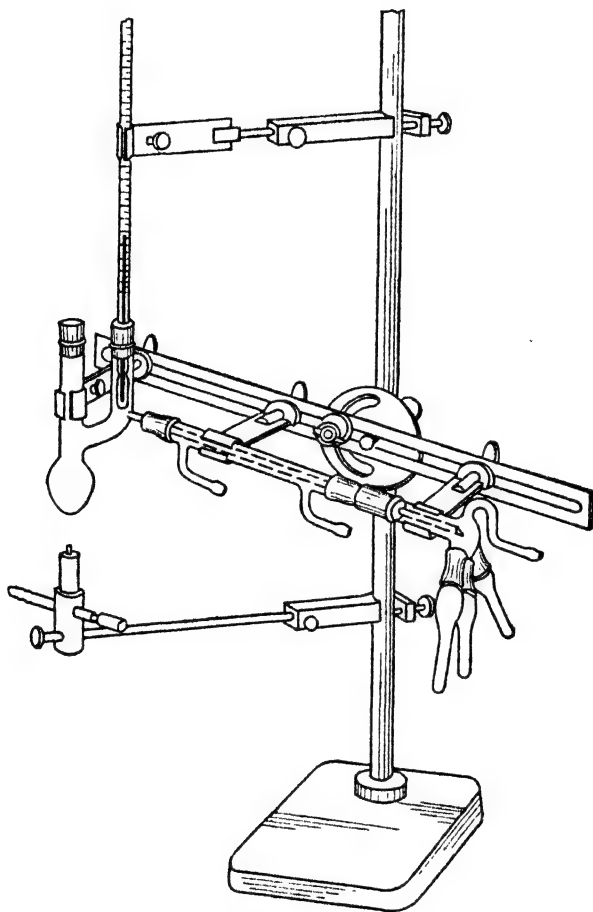



FIGURE 32
Bernhauer Vacuum Microdistilling Apparatus

the quantity of the liquid to be distilled is more than 1 ml. The side-arm connects through a ground joint to the condenser; the latter has at the lower end a three-way stopcock to direct the distillate from one tube to the other. The outlets attached to the stopcock are fitted with short pieces of Tygon tubing, which form a tight connection with the receiving tubes. The connection to the vacuum pump is on the upper part of

the condenser. When small amounts of liquid are distilled and each fraction consists of a few drops, it is necessary from time to time to release the pressure momentarily by opening a stopcock between the trap and the condenser in order to force each fraction into the receiver.

Determination of Boiling Points

One of the first objects in the preliminary examination of an organic liquid "unknown" is to determine whether it is a relatively pure com-

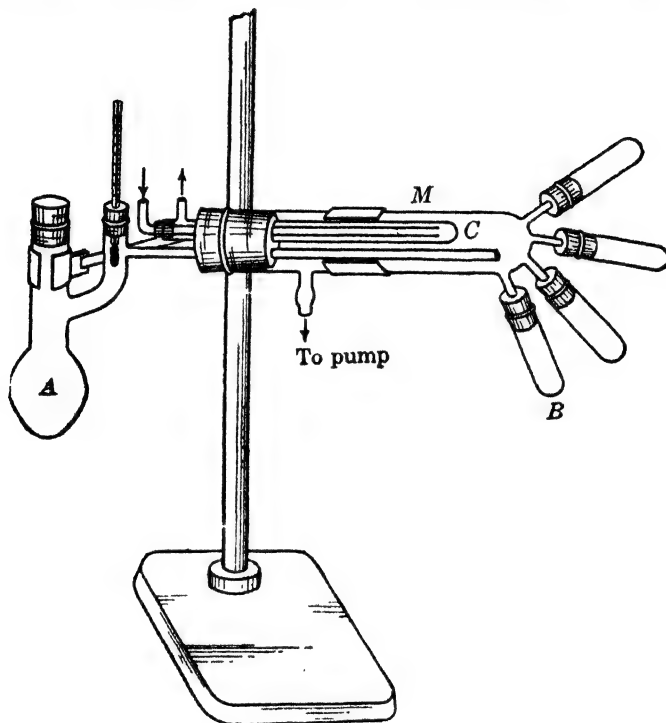



FIGURE 33

Semimicro Apparatus for Distillation under Reduced Pressure

A = 25- or 10-ml Claisen pear-shaped tube with 150-mm side-arm; *B* = receiving 3-ml tubes; *C* = microcondenser; *M* = manifold made from 8-inch tube with side-arm.

pound or a mixture. A simple distillation using 1–2 ml of the liquid will indicate whether it is: (a) a pure organic compound; (b) an organic compound containing a small amount of impurities; or (c) a mixture of organic compounds. A reasonably pure organic compound will distil within a temperature range of a few degrees; an impure compound will give a small amount of a "low fraction" or residue or both, but the main

fraction will distil within a small temperature range. In the distillation of nonazeotropic mixtures the temperature does not remain constant but rises slowly between the boiling points of the various components. In cases (a) and (b) the main fraction is collected for an exact determination of the boiling point. In the case of a mixture the various components are separated by fractional distillation and the exact boiling point of each component is ascertained. The boiling point of an organic compound[30] that boils without decomposition is one of the criteria used for tentatively identifying the "unknown."

FIGURE 34

Semimicro Fractionation under Reduced Pressure

Since the boiling point varies with the atmospheric pressure in the laboratory, the observed boiling point is not so reliable a criterion as the melting point. For very accurate work a correction is applied to the observed boiling point to reduce it to the corrected standard boiling point. For small deviations from 760-mm pressure the correction is a fraction of a degree. The rise in boiling points per millimeter increase in atmospheric pressure is approximately one ten-thousandth of the boiling point expressed in absolute degrees. The boiling point of benzene at 760 mm is 80.09°. The correction, therefore, for every millimeter deviation from 760 mm will be $(273 + 80) \times 0.0001 = 0.0353°$. For example, a sample of benzene, when boiled under a pressure of 750 mm, gave 79.7° as the observed boiling point. The correction is $(760 - 750) = 10 \text{ mm} \times 0.0353° = 0.35°$; the corrected boiling point is $79.7° + 0.35° = 80.05°$. It should be noted that this rule is only approximate and that it does not apply to pressures that are far removed from 760 mm.

In regions of high altitude and low barometric pressure the correction

[30] For detailed discussion of the boiling temperature of pure liquids, difference between boiling and condensation temperatures, and methods for their measurement consult, Swietoslawski in Weissberger *Physical Methods of Organic Chemistry*, Vol. I, Interscience Publishers, Inc., New York, 1945, pp. 47–63.

to be applied is of greater magnitude. The method is similar to that outlined for the calibration of thermometers. A number of pure liquids are selected that boil at various ranges. The boiling points of these liquids are determined as outlined below, and the differences between the observed boiling points and the boiling points recorded in the literature are ascertained. From these data correction curves are constructed.

The calibration of thermometers as given on page 32 provides the correction to be applied for errors due to thermometer construction and method of use. Most methods for the microdetermination of the boilings points employ the same apparatus as that used in the determination of boiling points. Of the many procedures that have been proposed, two will be described.

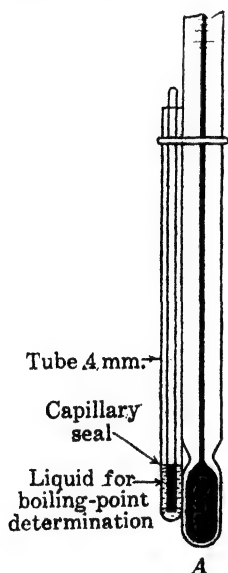



FIGURE 35

(A) Boiling-point Set-up with an Inverted Capillary; (B) Capillary for Boiling-point Determination, according to Emich

Procedure A. A glass tube, 4 mm in outer diameter and 80–90 mm in length, is sealed at one end and blown very slightly so as to form a minute bulb. About 2–3 drops of liquid, placed in this tube with a capillary pipette, will fill it to a height of from 7–8 mm. A melting-point tube, 1 mm in diameter and 70–80 mm in length, is inserted in the bulb with the open end downward in the liquid. The complete setup is attached to a thermometer as shown in Figure 35*A*. The thermometer is immersed in an oil bath, as in the determination of melting points. Heat is applied gradually; small bubbles of air trapped in the melting tube bubble out as the temperature rises. When the bubbles become rapid, the heating is discontinued, and the temperature is allowed to drop 5–10°; as the temperature drops, the liquid recedes into the melting-point tube. The temperature is raised slowly until a steady stream of bubbles emerges from the capillary. After the temperature has been noted, the heating is discontinued. When the liquid begins to recede into the melting-point tube, the temperature is again noted. This interval of temperature, which is very small in the case of a pure compound, is recorded as the boiling point.

Procedure B. This method[81] is particularly useful when the amount of

[81] Benedetti-Pichler and Spikes, *Introduction to the Microtechnique of Inorganic and Qualitative Analysis*, Microchemical Service, Douglaston, N. Y., 1935.

liquid for the determination is less than one drop. A capillary like that shown in Figure 35*B* is prepared. A piece of soft glass tubing 6–8 mm in diameter is heated above the blue cone of the flame while it is rotated continuously around its axis. When the tube is soft, it is removed from the flame and drawn out slowly so that a capillary pipette is obtained. Several of these pipettes are prepared, and one is selected that is about 100 mm in length, has a diameter of 0.5 mm, and tapers at the narrow point to 0.1 mm in diameter. The length of the narrow point should be about 10 mm. The narrow point of the capillary pipette is inserted in the liquid whose boiling point is to be determined. The capillary attraction forces the liquid to rise within the pipette. When the liquid has risen just above where the narrow point begins, the pipette is removed and held near the flame of a burner, with the tapered end pointing slightly upward so as to draw the liquid away from the narrow point. The point is heated momentarily at the edge of the burner so as to seal it. A small air bubble is formed and fills most of the fine point of the capillary. The bubble is examined with a magnifying glass to make sure that it does not extend into the tapered portion of the pipette.

The capillary pipette is attached to a thermometer as a melting-point tube and heated slowly in the bath. The air bubble is observed through a magnifying glass, a light being used if necessary. When the bubble begins to show signs of upward motion, the flame is removed. The temperature at which the bubble reaches the surface of the bath liquid is recorded as the boiling point of the liquid. After the bath has cooled to 10° below the recorded temperature, it is heated again slowly, and a second observation is made.

Value of boiling points. A knowledge of the boiling points of pure liquids is of value in identification work. When, through solubility and functional-group tests the compound has been restricted to a particular group, knowledge of the boiling point helps to exclude certain types and restrict the possibilities to a few compounds. If, for example, the tests indicate that the unknown is an alcohol and the boiling point is found to be 129–130°, inspection of Table 5, page 370, will confine the probability to those alcohols that boil between 128° and 131°.

Sublimation

Solids that have a high vapor pressure may be purified by sublimation; in this process the solid passes into the vapor state without melting, and, by appropriate arrangements, the distilled vapor is condensed to form crystals. The advantages of sublimation over crystallization are that

traces of solvent adhering to the crystals are eliminated and that the loss of material in purification is negligible.

An easy arrangement for microsublimation is by means of two watch glasses: a 50-mm watch glass is used as a heating vessel for the compound to be sublimed, and a smaller watch glass, 40 mm in diameter, is used as a condenser and receiver. About 1–5 mg of the compound is

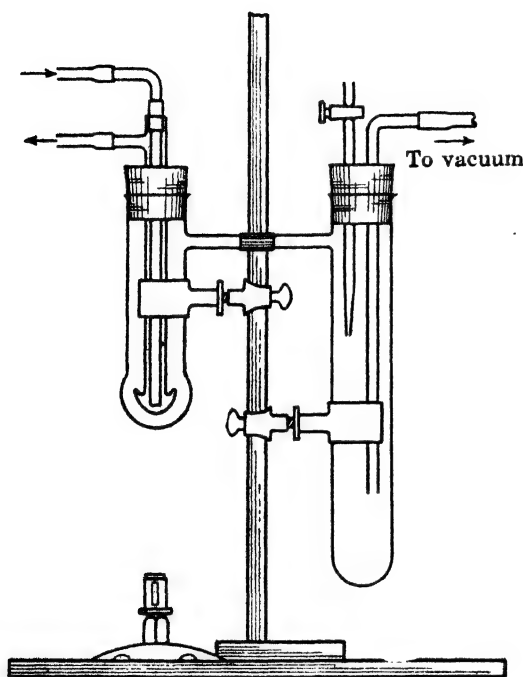



FIGURE 36

Apparatus for Microsublimation under Reduced Pressure

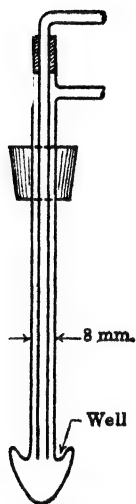



FIGURE 37

Special Microcondenser for Sublimation under Reduced Pressure

placed in the center of the larger watch glass and then covered with the smaller one. The microburner is placed at a distance of 100–150 mm from the wire gauze on which the sublimation apparatus rests, and the burner is adjusted to give a flame of about 20–25 mm in height so that the heating is slow. A filter-paper disc 25 mm in diameter is placed on top of the smaller watch glass and moistened with a drop of water at intervals. The sublimation proceeds slowly, and the apparatus needs no further attention except occasional moistening of the filter paper with a drop of water.

Figure 36 shows apparatus for microsublimation under reduced pressure. An 8-inch tube with a side arm is heated in an oxygen hot flame;

the lower part is drawn off, leaving a tube about 120 mm in length. The lower part is then blown out so as to bulge slightly and is later annealed. A No. 4 rubber stopper is thoroughly cleaned and fitted with a microcondenser. The stopper is inserted in the tube so that the end of the condenser is about 5–10 mm from the bottom. The tube connects by means of pressure tubing with another 8-inch tube of regular length. The two-hole rubber stopper that fits into this tube holds a glass stopcock and a glass tube bent into an L shape to connect to a water aspirator or mechanical vacuum pump. The solid to be sublimated is placed in the smaller tube, the various connections are adjusted, and evacuation started. Goggles should be worn throughout the subsequent operation. When the apparatus has been evacuated for about five minutes, the lower part of the tube is heated cautiously with a microburner, giving a small, semismoky flame. The sublimation begins almost immediately, and the crystals begin to creep up the sides of the tube until they collect at the end of the condenser. The rate of sublimation should be slow in order to obtain a mass of crystals that adhere well to the condenser. It should be noted that for efficient purification extremely slow sublimation is required. In this event a small flame is adjusted at a distance of 100 mm from the bottom of the tube and the substance is heated for 2–3 hours. When most of the solid has sublimed, the stopcock is turned very slowly to release the vacuum. The condenser is carefully removed by turning the sublimation tube in order not to disturb the crystals. If care is not exercised in this operation and if the sublimation was done rapidly, most of the crystals will dislodge themselves from the condenser and fall to the bottom of the sublimation tube. The condenser is held over a watch glass and the crystals are removed by means of the spatula.

Figure 37 shows a special microcondenser that may be used with the apparatus just described. The top of the condenser tube is curved upward to form a well. As a result of the application of heat against the wall of the tube opposite the condenser tip, the crystals creep upward and collect within the well of the condenser. In this way the dislodging of crystals from the condenser is avoided.

Determination of Refractive Indices

The absolute refractive index of a substance represents the ratio of the velocity of light in a vacuum to that in the substance. For the refractive index as commonly determined, air is used as the standard of comparison. The index is denoted by the letter n, with a superscript indicating the temperature of observation and a subscript denoting the

wave length of light used. Thus the refractive index of water = n_D^{20} = 1.3330 and n_D^{50} = 1.3290. The refractive index decreases as the temperature rises. The variation due to the temperature effect is different with various substances, but it may be approximated by taking the variation as 0.0004 per degree Centigrade.

The refractive index is one of the most important physical constants of organic compounds and can be determined accurately. As a criterion of the purity of liquids, it is more reliable than the boiling point. The determination of refractive indices is useful for the identification of an unknown organic compound. If the compound is pure, it is very valuable in excluding other compounds from consideration and often indicates the identity of the unknown.

Refractometers. There are several types of refractometers used for determining the refractive indices of liquids. The Abbe refractometer is widely used because it employs only a few drops of the material and requires but a few minutes for the determination. The Fisher refractometer has been introduced recently and is particularly adapted to the student's use. The Abbe refractometer, shown in Figure 38, consists of: (a) a pair of rotating water-jacketed prisms hinged together; (b) an observing telescope above the prisms for observing the border line of the total reflection that is formed in the prism; and (c) a sector on which the telescope is fastened. The sector is graduated from 1.300 to 1.710 and permits direct reading of the index of refraction; it is adjusted to the sodium D line of the spectrum.

FIGURE 38
Refractometer (Abbe)

This apparatus permits determination of refractive index to the fourth decimal place. For higher accuracy, use is made of the dipping refractometer.

(Eimer and Amend)

To operate the refractometer, the thermometer is adjusted in place, and the base of the prism enclosure is connected with a reservoir containing water at 20°. The left thumb is placed on the sector, and the right hand is used to open the double prism by pulling down the screwhead that is fastened on the lower prism. The prisms are wiped off carefully with a sheet of lens paper. (Facial tissue paper, such as Kleenex or Handies, are well adapted to the same purpose.) If the liquid is of a kind that

does not evaporate rapidly, two drops are placed on the face of the lower prism, which is closed immediately by means of the screwhead and clamped against the upper prism. If the liquid is volatile, the prism is closed; then the screw is slackened; and with a pipette dropper a few drops of the liquid are poured into the depression of the side of the prism leading through a narrow channel into the space between the two prisms. The screw is tightened and the prism is rotated by moving the arm at the side of the sector. The mirror is adjusted to obtain maximum illumination, and the cross hairs are brought sharply into focus. As the prism is rotated, the illuminated field is partly darkened by a shadow moving across it. The boundary between the dark and the light field is called the *dividing line*, or *border line*. If the dividing line is not sharp but is hazy with a band of colors, the compensator wheel, which is at the lower part of the observing telescope, is moved until the dividing line becomes sharp and colorless. The arm of the prism is moved until the dividing line coincides with the intersection of the cross hairs. The refractive index is read through the small eyepiece over the sector. The pointer indicates the last three figures of the refractive index. The first two are read on the left side of the scale a small distance below the pointer. The double prism is opened and cleaned with a piece of lens paper and a few drops of acetone.

The Fisher refractometer is shown in Figure 39*A*. A small glass slide with a beveled edge is fitted on the glass plate of the eyepiece, as shown in Figure 39*B*. A small clamp holds the glass slide down so that a prism-shaped well is formed between the plate of the eyepiece and the glass slide. The instrument has a cord by which it is attached to an electrical outlet. If the push button on the base of the instrument is pressed, and observation is made through the aperture of the eyepiece, an illuminated scale appears. The graduations on the scale are divided at 1.516 by an arrow. This point corresponds to the refractive index of the glass in the eyepiece.

When a very small drop of a liquid is placed in the well formed by the glass slide and glass plate of the eyepiece, the refraction of light passing through the prism of the liquid sample produces a secondary or virtual image of the arrow on the scale. A liquid having a refractive index less than that of the glass employed will cause the light to bend downward, and the secondary image will appear above 1.516 on the scale. Conversely, if the refractive index is higher, the bending is upward, and the secondary image appears below 1.516.

To operate the Fisher refractometer, the small glass slide is removed from the box and cleaned with lens paper. Likewise the plate of the

eyepiece is wiped off. The glass slide is placed with the beveled edge downward over the plate so that it just covers the aperture. The plug of the instrument is connected to an electrical outlet. A very small amount (0.01–0.05 ml) of the liquid is added at the edge of the glass slide directly over the aperture, by means of a capillary pipette dropper. The minute droplet spreads by capillary attraction over the beveled edge and fills the well. The push button is pressed, and the second arrow either above or below 1.516 on the scale is observed. This reading is the refractive index of the liquid. If the liquid evaporates rapidly, the droplet is added with one hand while the button is pushed with the other, and

A *B*

FIGURE 39

(A) Refractometer (Fisher); (B) Eyepiece of Fisher Refractometer

(A) Low cost renders instrument suitable for student use. Range: $n = 1.30$ to $n = 1.90$; permits estimation of refractive index to $n = 0.002$; (B) in the eyepiece there is a wedge-shaped well in which is placed a drop of liquid for the refractive-index determination.

(Eimer and Amend)

the secondary image is observed immediately. When the determination is completed, the glass slide is cleaned and replaced in the proper box. If it is desired to make several determinations, the glass slide and eyepiece are cleaned with lens paper between operations.

Table 2 lists a number of liquids commercially available[32] in uniform 25-ml glass-stoppered bottles that are suitable for practice in refractive-index determinations and also for the determination of the refractive indices of solids.

Refractive index of crystals. The determination of the refractive index of an *isotropic crystalline solid* is far more involved than the relatively

[32] Eastman Kodak Company, Rochester, N. Y.

easy procedure used for the determination of the refractive index of a liquid. Two general methods are in use: (a) particles of the crystalline solid are immersed into liquids of known refractive indices until a liquid is found in which a minimum visibility of the particle is obtained; then this liquid and the crystal are considered to have the same refractive index; (b) the particle is immersed in a medium having a lower refractive index, and a second medium that has a higher value is added for dilution

TABLE II

Liquids for Refractive Index Determination

SUBSTANCE	n_D^{20}	SUBSTANCE	n_D^{20}
Methyl alcohol	1.3288	Toluene	1.4957
Water	1.3330	Ethyl iodide	1.5138
Acetone	1.3592	Chlorobenzene	1.5250
Ethyl acetate	1.3727	Ethylene bromide	1.5466
n-Heptane	1.3872	*o*-Nitrotoluene	1.5466
n-Butyl alcohol	1.3991	Nitrobenzene	1.5526
n-Butyl chloride	1.4022	Bromobenzene	1.5602
Methylcyclohexane	1.4235	*o*-Toluidine	1.5725
Ethylene chloride	1.4453	Quinoline	1.6272
Cyclohexanol	1.4678	Aniline	1.5864
Triethanolamine	1.4853	*o*-Iodotoluene	1.6095
		s-Tetrabromoethane	1.6378
		α-Bromonaphthalene	1.6585

until minimum visibility is obtained. The refractive index of the diluted medium is then determined, and this value is taken for the refractive index of the particle. For *anisotropic crystalline solids* the method is still more involved, since the refractive index varies with the direction of transmission and the vibration of light in the specimen. The reader is referred to the literature references given in the Bibliography section. Of particular interest is the method proposed by Frediani,[33] who uses the Fisher refractometer to measure simultaneously the melting point and the refractive index of the resulting liquid.

Uses of refractive index. As previously mentioned the refractive index is of value in the examination of the composition of liquids. In most cases the examination of the refractive index of several fractions from the distillation of the liquid will indicate whether one is dealing with a mixture or a pure substance. In the fractional distillation of a mixture of two or more liquids, the refractive index may be used to determine the composition of the distillate when the components of the mixture have boiling points that are close together. Finally, the refractive index, to-

[33] Frediani, *Ind. Eng. Chem., Anal. Ed.*, 5, 439 (1942).

gether with the boiling point or melting point of the substance, density, and other physical data, are of aid in restricting the possibilities as to the probable nature of the unknown. In many cases, particularly in dealing with isomeric substances having boiling points close together, the refractive index is invaluable in eliminating several of the isomers.

Of theoretical interest is the fact that the refractive index, together with the density, may be used in calculating the *molecular refractivity*, using the equation of Lorenz and Lorentz. The reader is referred for discussion of this topic to a text in physical chemistry.

Optical Rotation

Although the number of organic compounds that exhibit optical activity is quite large, the determination of specific rotations for identification work is most useful in the characterization of carbohydrates.

The polarimeter. Figure 40 shows a diagram of a simple polarimeter for general use. The light employed in making the measurement of

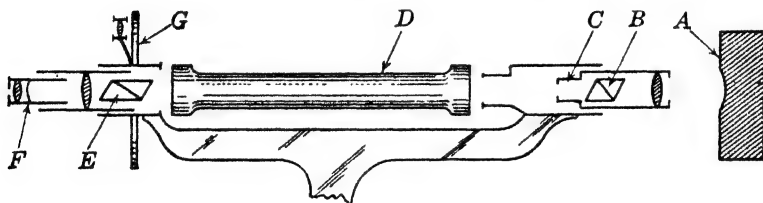



FIGURE 40
Diagram of Polarimeter

optical rotation is the monochromatic light of a sodium flame and is obtained by placing a piece of fused sodium chloride in the flame or from an electric sodium-vapor lamp. The light from flame A passes through the polarizing Nicol prism B. A plate of quartz, cut parallel to the optic axis, covers half the opening C, and is of such thickness that it produces a difference of a half wave length between the two rays it gives off by double refraction. The light then passes through the substance, which is placed in the tube D and strikes the analyzing, movable Nicol prism E. The telescope F is focused on the edge of the quartz plate at C. If the prism E is turned, a pointer moves over the graduated circle G, indicating the angle through which the prism was moved. When the tube is filled with a nonrotating liquid—pure water, for instance—and placed between the two prisms, the light passing through, because of the construction of the instrument, will produce different intensities of illumina-

tion in the two halves of the field, as shown in Figure 41. The movable prism is turned until uniform illumination is obtained. This is the zero point of the instrument (Figure 42). When the tube is filled with an optically active liquid, or the solution of an optically active substance, and placed between the two prisms, the light rotates through a certain angle. It is necessary to move the prism C through an angle equal to the angle of rotation in order to establish uniform illumination again. The angle of rotation varies with the length of the column of liquid in the tube. For comparison, the specific rotation is defined as the angle of rotation produced by one gram of an active substance in one cubic centimeter by a layer one decimeter in length.

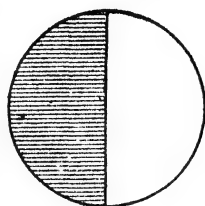



FIGURE 41
Field of Polarimeter
(Illumination in Two Halves)

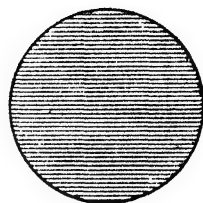



FIGURE 42
Field of Polarimeter
(Uniform Illumination)

For sodium light (D line, 5,890 Angstroms wave length) the specific rotation (α) is calculated by the use of the following formula, applicable to solutions of pure liquids and compounds:

$$(\alpha)_D = \frac{\alpha \times 100}{L \times c}$$

where α is the observed rotation of the sample in degrees, L is the length of the tube in decimeters, and c is the concentration of the dissolved active substance per 100 ml of solution. For the determination of the specific rotation a definite weight (100–500 mg) of the pure substance is dissolved in a volumetric flask and diluted to known volume. The tube is filled and the rotation of the sample is measured. Dilutions from this solution are made, and again the rotation is measured. From the observed rotation of various concentrations the specific rotation is calculated. The variation between the figures obtained by using different concentrations should be small.

For pure liquids the same formula may be used with the following changes. The number 100 is eliminated from the numerator, and c is changed to d = density in the denominator.

Modern polarimeters. Polarized light is produced through double refraction by Nicol prism in the polarimeter described above. Another method of producing polarized light is by absorption. Certain substances have the characteristic of absorbing ordinary light partially and producing plane polarized light with about half the original intensity.

A material of this type is *Polaroid* sheeting, which consists of a transparent plastic sheet in which are closely embedded a layer of fine needle-shaped crystals of iodoquinine sulfate. Sheets of Polaroid laminated between glass may be used for the construction of the polarizer and analyzer. Some modern polarimeters are constructed on this principle. This type of instrument is simple to operate, moderately priced, and is recommended for beginners.

Preparation of the solution. About 200–500 mg of the substance are accurately weighed and dissolved in 25 ml of the solvent in a volumetric flask. The solvents commonly used are water, methanol or ethanol, chloroform and a mixture of ethanol and pyridine. For the rotations of hydrazones and osazones the method recommended by Neuberg[34] requires 200 mg of the derivative dissolved in a mixture of 4 ml pyridine and 6 ml absolute alcohol, and a reading of the solution in a 100-mm tube.

The compound must be purified before the solution is prepared. If the solution is not clear, it should be filtered after being properly diluted. The filtrate is collected in a dry flask and is returned to the funnel until a perfectly clear filtrate passes through the stem. The funnel is placed over another dry flask and the clear filtrate is collected for the determination.

Observed rotation. The tube is held vertically and the solution is poured in until it rises to the top end; the cover glass is placed over the end of the tube in such a manner that no bubbles appear. The cap is screwed on the tube with care. If great pressure is applied to the cover glass, the strain may produce optical activity and a serious error will be introduced in the observation.

The *zero reading* of the instrument is determined by turning the movable prism until the two halves of the field have a uniform illumination (Figure 42). Before the two fields are matched, the eyepiece of the telescope *F* should be checked for focusing; this is accomplished by turning the eyepiece to the right or left until the line that divides the two fields is sharp. The true zero of the instrument may not coincide with the zero of the graduated circle. Five readings are made and the values averaged. The polarimeter tube that contains the solution is placed between the two prisms (position *D*). The movable prism is turned until uniform illumination is obtained. The reading of the circle is noted and the observation is repeated 4 or 5 times. The temperature at the time of the readings is recorded. The values of the readings are aver-

[34] Neuberg, *Ber.*, 32, 3384 (1899).

aged; this average rotation less the zero reading gives the observed rotation. The specific rotation is calculated from this value.

Determination of Density[35]

The determination of density is useful in the identification of compounds that do not form well-defined derivatives. The characterization of such substances as the liquid aliphatic hydrocarbons is usually accomplished through determination of the boiling points, refractive indices and densities. The determination of density may also be used as a general index of the relative complexity of the unknown. Compounds that have a density of less than 1.0 usually do not contain more than one functional group, whereas polyfunctional compounds have as a rule a density greater than 1.0.

The difficulties encountered by beginners in the accurate determination of the densities of organic liquids account for the restricted use of this important physical constant. Compared with the determination of melting points, refractive indices, and boiling points, the measurement of densities is subject to more errors because *simple*, *rapid*, and *reliable* instruments and techniques have not yet been developed. The macromethods that use 1–5 ml of liquid are reliable if proper pycnometers are used and sufficient time is available for repeated accurate weighings with an analytical balance. The micromethod described in this section gives reliable results if care is exercised. Since the amount of liquid for the determination is 0.02–0.03 ml, small errors in weighing or losses by evaporation will cause large discrepancies. For determination of the densities of *solids* the reader is referred to the literature.[36]

Macromethod pycnometers with a capacity of 1–2 ml are commercially available. The pycnometer is cleaned, dried, and then weighed. The bulb is then filled with distilled water to a point above the mark and immersed in a 25-ml beaker containing water at 20°. After 5–10 minutes the level of water in the pycnometer is adjusted by means of a capillary pipette dropper. The pycnometer is then removed from the beaker, dried rapidly with a small piece of chamois and weighed. The pycnometer is then emptied, dried, and filled with the liquid under investigation; it is adjusted at 20° as before, and weighed. The weight of the sample divided by the weight of water gives the density of the liquid at

[35] For extensive discussion of the measurement of density of liquids consult Bauer in Weissberger *Practical Methods of Organic Chemistry*, Vol. I, Interscience Publishers, New York, 1945, pp. 77–86.

[36] Sullivan, *U. S. Bur. Mines, Tech. Paper*, **381** (1927); Caley, *Ind. Eng. Chem., Anal. Ed.*, **2**, 177 (1930); Blank, *ibid.*, **3**, 9 (1931); Blank and Willard, *J. Chem. Educ.*, **10**, 109 (1933).

20°. However, the density of water at 20° is not 1.0000, and therefore a correction must be made to express the density with reference to that of water at 4° by the following factor:

$$D_4^{20} = \frac{\text{Weight of sample}}{\text{Weight of water}} \times 0.99823$$

Micromethods. The Alber specific-gravity pipettes[37] that are commercially available[38] may be used for the microdetermination of densities. The *A* type pipette has a bore of 0.5 mm and is suitable for volumes of 0.005–0.016 ml; the type *B* pipette is designed for volumes of 0.02–0.08 ml. Both sizes have a graduated scale 80 mm long in 1 mm divisions. The pipette is calibrated at four or five points, by the use of a heavy liquid such as Bromoform. Both ends of the pipette are sealed through ground glass caps; this permits an accurate determination of the densities of minute volumes of highly volatile or hygroscopic liquids.

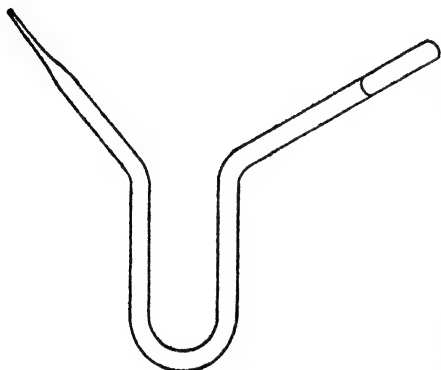



FIGURE 43
Pycnometer of 3-mm Tubing

Semimicro and microdeterminations of density may be made by the beginner through pycnometers that are easily constructed of 3 to 4 mm-tubing or glass capillaries. The pycnometer shown in Figure 43 is made of 3-mm glass tubing and has a capacity of 0.2–0.4 ml; the pycnometer

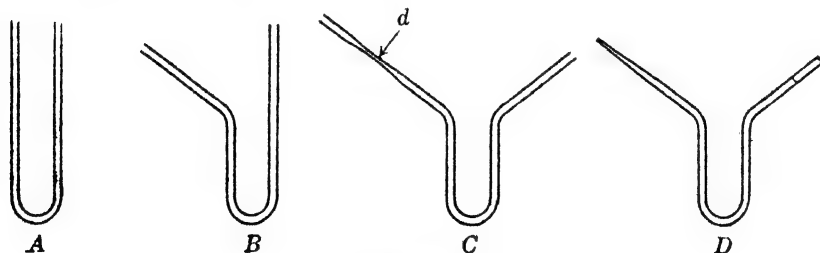



FIGURE 44
Construction of Capillary Pycnometer

in Figure 44 is made from a melting-point capillary and requires about 0.02–0.03 ml for a determination.

[37] Alber, *Ind. Eng. Chem., Anal. Ed.*, **12**, 764 (1940).
[38] Arthur H. Thomas Co., Philadelphia, Pa. Apparatus Nos. 9036B and 9036D.

The capillaries used for making the pycnometers are first heated in chromic acid mixture, then thoroughly rinsed with water and dried. A melting-point capillary tube 70–80 mm in length and 1–1.2 mm in diameter is heated cautiously over a very small flame of the microburner and first bent into a hairpin shape as shown in Figure 44*A*; one side of the hairpin is then bent as shown in Figure 44*B* by heating the capillary cautiously 14–15 mm from the bend. The other side of the hairpin is similarly bent into the shape shown in Figure 44*C*. The flame is then directed against one of the arms about 15 mm from the end, at point *d* of Figure 44*C*. When the glass is soft, it is slowly drawn out so that it forms a constriction of 0.5 mm; after a few seconds the glass is broken at the constriction. The broken end is momentarily heated to round off the edges of the glass, care being taken that the opening does not become closed. The final form of the capillary pycnometer is shown in Figure 44*D*. The edge of the spatula is dipped into white ceramic ink[39] and a mark is made about 5 mm from the end of the long arm of the pycnometer; the ink is dried by moving the arm over a small flame for a few seconds. The pycnometer is suspended by means of a fine copper, nichrome or aluminum wire and its weight determined. The pycnometer is then filled with water beyond the mark by touching the constricted arm to the surface of a small test tube filled with water that has been previously cooled to 20°. Capillary attraction forces water into the pycnometer rapidly, so that only a second or two is required for the operation. The amount of liquid in the capillary pycnometer is adjusted by touching the constricted tip against a filter paper until the meniscus in the long arm coincides with the mark. The pycnometer is then wiped with a dry piece of chamois and weighed as rapidly as possible. It has been found that if the capillary is filled with a liquid at 18° and the temperature of the room is at 20–22°, the pycnometer with its contents acquires that temperature rapidly. The alternative is to immerse the capillary pycnometer in a bath at 20° and then after 5 minutes adjust the meniscus and wipe off the pycnometer.

The capillary pycnometer is emptied by holding the constricted tip against a filter paper and is then filled first with alcohol and then with ether, and dried by heating in an oven. The pycnometer is then filled with the liquid under investigation, which has been previously cooled at 20°, and its weight determined. From the data obtained the density is calculated as shown in the preceding section.

[39] Wilkens-Anderson Co., Chicago, Ill.

Weighing and Measuring for Semimicro Work

Weighing. The horn-pan hand balance shown in Figure 45 and the triple-beam balance[40] shown in Figure 46 have been found satisfactory for weighing samples of 10 mg to several grams. Since beginners in semimicro work seldom use quantities of 1–10 mg, either of these balances will suffice. The triple-beam balance has a capacity of 200 g and has the advantage of not requiring a set of weights. The type of balance shown in Figure 46 has a mechanism for arresting the swing of the beam, thus permitting rapid and fairly accurate weighing. Solids are weighed on pieces of glazed paper. An ordinary 8.5 x 11 sheet of paper is folded and cut in eight equal pieces, which are suitable for weighing 50–500 mg of solids. For quantities of 1–5 g the 8.5 x 11 sheet is cut into four equal pieces. A piece of paper is placed on each pan of the horn-pan balance and counterbalanced if necessary by adding small bits of paper to one pan or the other. When the triple-beam balance is used, a single piece of paper is first weighed and then the proper weights are added. The solid is placed on the paper with a spatula, care being taken not to spill any solid on the pan of the balance. After weighing, the paper on which the solid was placed is washed with water and thrown in the waste jar.

FIGURE 45
Horn-pan Balance
(Schaar and Company)

Weighing of solids or liquids directly in the 6-inch or 8-inch tubes is easily accomplished by means of the *weighing rings*. To make a weighing ring, take a piece of number 20- or 22-gauge iron or copper wire 200 mm in length and wrap two loops around the test tube under the lip. Twist the two ends of the wire together twice and cut one end near the loop. Bend the other end at right angles to the loop so that it projects upward about 30 mm; bend the end of the single wire into the form of a hook. The ring becomes suspended at the lip.

The hook of the ring is then inserted at the support from which the pan

[40] Schaar and Co., Chicago, Ill. Apparatus No. 577.

of the balance is suspended from the beam. The tube and ring are counterbalanced by means of weights and then the proper quantity of solid or liquid is added to the tube. Small quantities of liquids are at times more easily weighed than measured. A small amount of liquid is poured into a 25-ml beaker and by means of a pipette dropper the liquid is weighed, adding a drop at a time. It is advisable to have two rings each for 6-inch and 8-inch tubes. If iron is used for the rings, it should be lacquered, to prevent rusting.

FIGURE 46
Triple-beam Balance
(Schaar and Company)

For weighing samples of 0.5–10 mg either the Salvioni-Alber type of balance or a rough quantitative balance may be employed. Figure 47 shows the Salvioni-Alber spring-action balance.[41] The balance consists of a spiral-shaped steel spring having a V-shaped notch near the free end. An aluminum pan 3 mm deep and 10 mm in diameter to hold samples is suspended from the V-shaped notch. The weight is indicated by the deflection, under load, of the spiral spring and is measured on a direct index scale. The range of the index scale is 0–25 mg in 1-mg divisions; the zero adjustment and compensation for taring the weighing pan are accomplished by a lever arm attached to the bar that supports the spring. The sensitivity of this type of balance is 0.3 mg with full load or 0.1 mg with 1-mg samples. It is useful in weighing samples of 0.5–10 mg.

FIGURE 47
Salvioni-Alber Spring Balance
(Arthur H. Thomas Co.)

Measurement of liquids. Graduates of 10-ml capacity graduated in 0.1 ml are commercially available. However, for most work the measure-

[41] A. H. Thomas Co., Philadelphia, Pa.

ments of liquids is accomplished by means of droppers. Practically all solvents and reagents used in semimicro work are dispensed in the authors' laboratories from reagents bottles having a capacity of 15 or 30 ml and provided with a plastic cap holding a glass dropper and rubber bulb.[41,42] The glass droppers have a tip about 2.5–3 mm in outer diameter and deliver approximately 0.5 ml of liquid if the rubber bulb is pressed on the upper part.

For the measurement of liquid reagents the weight of each drop is of considerable importance. The chief factors determining the weight of a drop of liquid are: (a) the outside diameter of the dropper at the tip; (b) the surface tension of the liquid; and (c) the density of the liquid. Most commercial droppers have a tip with an outside diameter close to 3 mm. Measurement of 48 droppers of about 100 mm length from four different manufacturers disclosed only one dropper with a tip diameter of 2.7 mm and one with 4.0 mm; the 46 droppers had tips with diameters between 2.9 mm and 3.2 mm. The graduated pipette droppers[42] developed by the authors have tips with a diameter of 2.6–2.8 mm.

Table III shows the influence due to the diameter of the orifice of the dropper. Three droppers were selected for this series of experiments. The first dropper, with a tip 2.4 mm in diameter, represents the average from the droppers of the semimicro reagent bottles. The second dropper with a tip of 3.0 mm represents the average from the commercial droppers. The third dropper, which has a tip of 4.0 mm, represents an extreme case of the commercial dropper. The results indicate that large errors are introduced by measuring reagents in drops unless such information as shown in Table III is available.

In general, the measurement of solvents is only approximate; for example, if it is desired to wash a derivative with 1 ml of 50 per cent methanol, no serious error is introduced by the use of one dropperful (from the semimicro reagent bottle) of methanol and one dropperful of water. If the amounts are calculated from the data given in Table III, the volume of the alcohol-water mixture produced is 1.3 ml, containing 50 per cent alcohol by weight. On the other hand, however, the measurement of liquid reagents should be as accurate as possible. If calibrated droppers are not available, two or three may be calibrated in a short time. A convenient method is to take off the rubber bulb of the dropper, close the outlet by means of a little paraffin wax, then deliver by means of a 1-ml pipette (graduated in 0.1 ml) 0.5 ml. After this a mark is made by means of white ceramic ink; then another 0.5 ml portion is added and marked; finally, the pipette is drained and heated slightly

[42] Wilkens-Anderson Co., Chicago, Ill.

over a free flame to dry the ink. If it is desired, a mark can be made to indicate delivery of 0.25 ml.

TABLE III

Measurement of Liquids by Droppers

INFLUENCE OF DIAMETER OF ORIFICE

LIQUID	DENSITY	DROPPER A DIAMETER 2.4 MM		DROPPER B DIAMETER 3.0 MM		DROPPER C DIAMETER 4.0 MM	
		I[a]	II[b]	I[a]	II[b]	I[a]	II[b]
Water	1.000	25	16	22	25	17	20
Methanol	0.792	75	44	65	50	50	40
Ethanol (95%)	0.816	75	44	65	50	48	40
Ethyl ether	0.708	100	41	88	70	64	49
Acetone	0.792	70	36	60	45	48	42
Benzene	0.879	60	40	55	56	40	44
Bromobenzene	1.495	50	45	45	73	34	61

[a] Number of drops per gram of substance.
[b] Number of drops delivered by dropper by filling it with a single pinch on top of the rubber bulb.

Pipette droppers with long capillary tips. In the separation of small volumes of immiscible liquids, and in delivering quantities less than 0.1 ml, pipettes with long capillary tips are extremely successful.

To prepare a pipette, clean thoroughly with soap and water a piece of soft glass tubing 200 mm in length and 6–8 mm in diameter. Rinse well first with tap water and then with distilled water. Allow it to dry. Use either a good Bunsen flame, or, if not familiar with elementary manipulations, use a burner provided with a wing top. Grasp the ends of the glass tubing with both hands and rotate it between the thumb and index finger over the flame. When the glass has softened enough to bend easily, remove from the flame and draw gently and steadily lengthwise until the length has doubled. Hold in place until the glass has hardened and then lay it carefully on an asbestos mat. The capillary is then cut in about the middle. Heat the wide end of the pipette until it is fire polished. If the glass tubing used is of 6-mm bore, the wide end should be flanged in order to form a tight fit with the rubber bulb. To flange the end, heat it in the flame until the tube has softened; then press firmly against an asbestos pad. The operation is repeated until a flange 7–8 mm in diameter is formed. Pipette droppers of various sizes are made by a method similar to that described for the capillary pipette.

Burners and heating baths. Figures 48–50 show various types of burners for micro- and semimicro work. The Thomas, Fisher, and Waco

FIGURE 48
Thomas Microburner
(Arthur H. Thomas Co.)

microburners have been found satisfactory for most operations. Most college laboratories are equipped with semimicroburners for qualitative inorganic analysis; these may be used for most operations. Whenever a very minute (nonluminous) flame is required, a microburner constructed from glass tubing, as shown in Figure 51, may supplement the semimicroburners.

Beakers of 125-ml and 250-ml capacity may be used as water-heating baths in semimicro work. Small tin cans 2–3 inches in diameter will serve the same purpose without any danger of breakage.

A three-purpose heating bath, especially developed for semimicro work in organic chemistry, is shown in Figure 52. The bath is made of metal and is 70 mm in depth and 90 mm in diameter. The top is detachable but fits snugly so that no vapors can leak through it. The top has four holes provided with short rings to support the distilling tubes. There are two openings of 20 mm in diameter for 6-inch tubes, one opening 26 mm in diameter and one 35 mm in diameter. The two large openings are suitable for holding 8-inch tubes. The openings are stoppered by corks (Nos. 8, 14, and 20) to convert this type of water bath to a steam distillation apparatus as directed on page 50.

FIGURE 49
Fisher Microburner
(Eimer and Amend)

Figure 53 shows the Clark[43] Electric Sand Bath.[44] It consists of a rectangular corrosion-resistant metal tray with a deep ledge on four sides, mounted in an insulated support containing a heating element. The tray is filled with silica sand. The temperature of the sand at the surface increases from the sides to the center and also with the depth of penetration. The bath is convenient for the rapid heating, refluxing, and evaporation of small samples.

FIGURE 50
Waco Microburner
(Wilkens-Anderson Co.)

[43] Clark, *J. Assn. Off. Agr. Chem.*, **16**, 418 (1933).
[44] Arthur H. Thomas Co., Phila., Pa. Apparatus No. 8866 K.

Evaporation. For the evaporation of mother liquors or for the concentration of dilute solutions, the pear-shaped flask shown in Figure 54 is useful. Flasks of 5-, 10-, and 25-ml capacity are commercially avail-

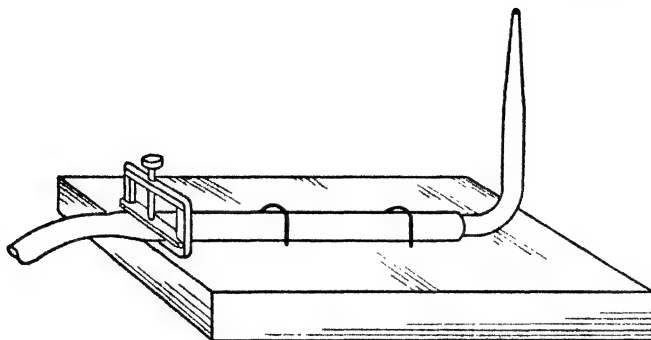



FIGURE 51
Glass-tube Microburner

able.[45] The flask is fitted on one of the openings of the water bath described on page 78; an 8-inch tube containing about 10 ml of water may serve as a water bath for the two smaller flasks. A few boiling stones are added in the tube and heat is applied by means of a small flame so that the water boils gently. For evaporation at reduced pressure, the ar-

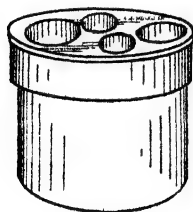



FIGURE 52
Heating Bath

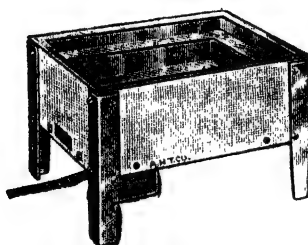



FIGURE 53
Clark Electric Sand Bath
(Arthur H. Thomas Co.)

FIGURE 54
Pear-shaped Flask

rangement shown in Figure 55 may be used. The flask is fitted with a rubber stopper carrying a microcondenser with the lower end open and the inner tube drawn to a pointed capillary. The upper end of the inner tube is connected by means of rubber tubing to a calcium-chloride tube.

[45] Wilkens-Anderson Co., Chicago, Ill. Apparatus No. 3672-A.

The stream of dry air admitted through the tube is regulated by means of a screw clamp; the distance of the capillary from the surface of the liquid is adjusted so that, when air is drawn, a ripple is produced.

Separation of immiscible liquids. Separatory funnels of 30- and 60-ml capacity may be used for the separation of semimicro quantities of two immiscible liquids. The pear-shaped 60-ml *separatory funnel* is recommended for all-around work. Another arrangement for the separation of small quantities of immiscible liquids is the *separatory stopper*. Stoppers may be made to fit a 3-, 6- or 8-inch tube. This method requires greater skill in manipulation than the operation of a separatory funnel, but it is useful when the latter is not available. The following detailed directions for construction of separatory stoppers are intended for beginners.

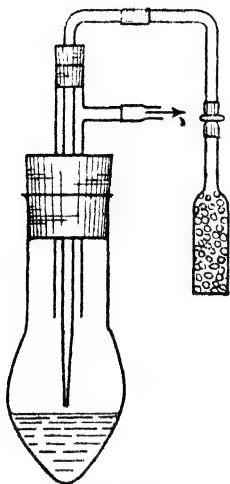



FIGURE 55
Evaporation at Reduced Pressure

Separatory stoppers. To make a stopper for a 6-inch tube, cut a piece of 4-mm glass tubing 220 mm long and rotate each end over the flame until the opening is reduced to a fifth of the original size. Insert the tube through one of the holes of a No. 2 rubber stopper so that the latter fits tightly in the mouth of the tube, and the end of the glass tubing barely avoids touching the bottom. Insert the other end into a 30-mm piece of 3-mm rubber tubing. Through the other hole of the rubber stopper insert a piece of glass tubing 40 mm long, so that it just reaches the other side of the hole but does not protrude through it. This short glass tube is connected through a piece of 3-mm rubber tubing 300 mm in length with the delivery tube. The delivery tube is a piece of glass tubing 35 mm in length and drawn out into a capillary, similar to that used for washing bottles. Finally a screw clamp is placed at the middle of two pieces of rubber tubing. A pinchcock clamp may be used, if the capillary of the delivery tube is drawn out so that the opening is smaller. The complete assembly of the separatory tube is shown in Figure 56*A*.

To make a stopper for an 8-inch tube use a piece of glass tubing 4 mm in diameter. The long piece of glass tubing is 280 mm in length, the short pieces about 40 mm in length. A two-hole No. 5 rubber stopper is used. The other directions are the same as those for the separatory stopper for 6-inch tubes.

Separation by means of separatory stopper. Figure 56*A* shows diagrammatically the separatory stopper inserted into a tube, thus completing the separatory tube.* Figures 56*B* and 57 show the separatory tube in use for the separation of two immiscible liquids. The separatory stopper may be inserted in any tube containing two immiscible liquids to

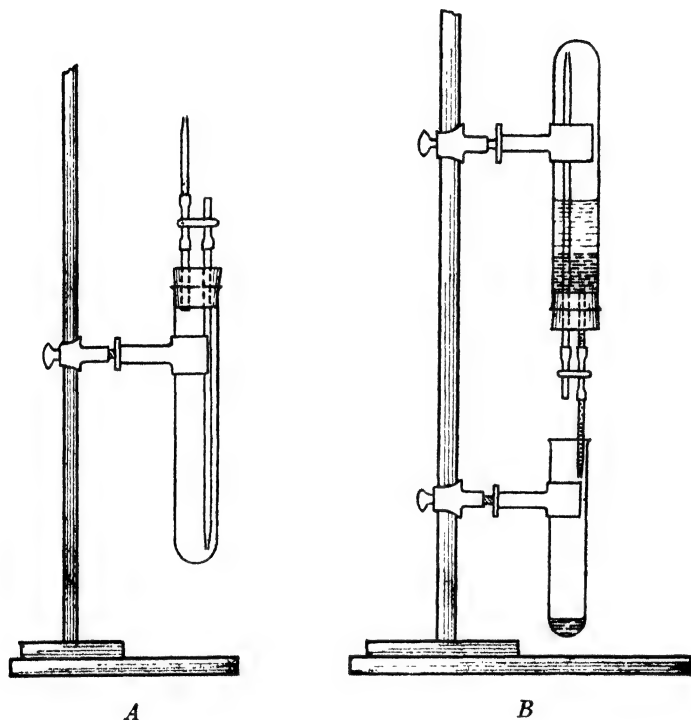



FIGURE 56

(A) Separatory Stopper and Tube for Separation of Immiscible Liquids; (B) Semimicro Separatory Tube in Use.

be separated. In order to separate the two layers the screw clamp is closed tightly, and the tube is inverted and held in such a way that the rubber stopper rests between two fingers of the left hand with the thumb pressing lightly upward upon the lip of the tube. The delivery capillary tube is placed inside a clean test tube, and the screw clamp is operated with the right hand. When the interface of the two layers nearly reaches the rubber stopper, the flow is diminished; and, when the junction of the two layers appears in the capillary tube, the flow is stopped. The separatory tube is placed in an upright position, still pressing on the rubber stopper. With a slow sidewise motion loosen the stopper so as to

release any pressure. Raise the stopper about 1 mm, and loosen the screw clamp so as to return the liquid in the delivery tube to the liquid within the test tube. Care should be exercised not to raise the stopper too far and not to tilt it so that the liquid within the capillary tube will fall outside of the test tube. Since the amounts handled in semimicro work are small, loss of a few drops is serious. It is suggested that the beginner practice a little with 3 ml each of water and benzene, or water and kerosene. The separatory stoppers, after use, are cleaned and placed in a box so that they may always be ready. For separation of 2 ml or less of two immiscible liquids a pipette dropper with long capillary tip (page 77) is more efficient than a separatory funnel or the arrangement of a tube with the separatory stopper. The bulb of the dropper is pressed and the capillary tip is inserted into the tube until it reaches 1–2 mm above the junction of the two liquids. The pressure on the bulb is then released gradually until the upper layer has been withdrawn.

FIGURE 57
Operation with One Hand of Semimicro Separatory Tube

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[46] Wherever feasible, the references in all bibliographies have been arranged in chronological order.

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CHAPTER 3

Preliminary Steps in the Examination of Organic Compounds

The first step in the identification of organic compounds is to ascertain whether the material under investigation is a pure substance or a mixture (see page 10). If the unknown is a pure substance, a few preliminary tests are made before the qualitative analysis for elements, because such tests often serve as guides to subsequent work.

3.1 Gross observations. The *color*, *odor*, and *crystal structure* are noted during the preliminary steps in determining the purity of the material under investigation. To a person who has had considerable experience with organic compounds, these observations may give a clue as to the probable nature of the unknown and may shorten considerably the work involved in the identification. For example, phenol, cresol, thymol, the lower aliphatic acids, most amines, aldehydes and a host of other organic compounds have characteristic odors that can be easily identified by an experienced person. Frequently the color of the material will also give important information. Yellow color is associated with the presence of nitro groups. Quinones, azo compounds, and many derivatives of triphenylmethane and anthraquinone are colored. Color due to impurities usually diminishes or disappears upon purification. It is advisable, however, for the *beginner to proceed systematically through all the steps*, taking note of all the gross characteristics. As experience is gained, it will be possible to utilize curtailed procedures and short-cut methods.

3.2 Ignition test. The ignition test makes it possible to observe the behavior of the substance on combustion. Organic compounds containing metals, such as the salts of carboxylic acids, sulfonic acids, and the like, leave a residue consisting mainly of the carbonate of the metal. Aromatic compounds burn with a smoky flame, whereas the lower aliphatic ones give an almost nonsmoky flame. Compounds containing oxygen burn with a bluish flame. Sugars and proteins burn with characteristic odors. Halogen compounds burn with a smoky flame; polyhalogen compounds, however, as a rule do not ignite until the flame is applied directly to the substance, which then momentarily renders the flame of the burner smoky.

The inside of a porcelain crucible cover or a small evaporating dish

may be used to ignite a small amount of the substance. The evaporating dish or the crucible cover may be heated directly. About 1–2 mg of the substance are placed near the center of the vessel and heat is applied gently by means of a small flame. From time to time the flame is applied directly to the top of the substance so that it will ignite before it volatilizes. If the substance carbonizes, the flame is increased and finally the substance is strongly heated. If a residue remains, it should be nearly white. If gases are given off in the initial stage of heating—that is, before ignition—a test should be made by means of litmus or *p*H paper to determine whether the gas has acidic or basic properties.

3.3 Presence of water. The presence of water in organic liquids is usually detected in the purification of the unknown; traces of water, however, may escape detection. It is important that appreciable amounts of water should not be present in several tests, such as those for sodium fusion and detection of hydroxyl groups. If water is found to be present, it should be removed before further tests are made.

For the detection of traces of moisture in liquids, about 50 mg of anhydrous copper sulfate (colorless) are placed on a watch glass and a drop of the liquid to be tested is placed so as to cover the copper salt. If water is present, it will hydrate the salt to the blue pentahydrate. Another method for the detection of traces of water is to add to a few drops of the liquid a small amount of aluminum ethoxide; the presence of water is indicated by the appearance of gelatinous aluminum hydroxide. Appreciable amounts of water are detected by adding a very small crystal of potassium permanganate to 0.5 ml of the liquid in a test tube; the liquid acquires the characteristic violet or purple color of permanganate solutions.

Active unsaturation. Unsaturated compounds that are readily oxidized and undergo addition of other groups easily are designated as having *active unsaturated linkages.* Such linkages are oxidized rapidly by aqueous permanganate solutions; the permanganate ion is reduced, as shown by the rapid disappearance of the purple color of permanganate ion and the appearance of the brown-colored hydrated oxide of manganese. Similarly the rapid decolorization of a 1–2 per cent solution of bromine in carbon tetrachloride without the evolution of hydrogen bromide is an indication of an addition reaction of bromine with an unsaturated linkage.

3.4 Permanganate test (Baeyer's test). About 50–100 mg of the compound to be tested are dissolved in 2 ml of water, alcohol or ether, and two drops of 1 per cent aqueous potassium permanganate are added. The rapid decolorization of the purple solution indicates the probable

500 mg of anhydrous sodium carbonate and placed in a Pyrex test tube. A glass rod is inserted through a slotted one-hole cork and fitted into the tube so that the end is about 15 mm above the surface of the sodium carbonate mixture. The end of the rod is coated with a mixture of equal parts of powdered cuprous iodide and water. With the tube held at an angle of 45° its lower end is heated gently over a small flame. In the presence of mercury the cuprous iodide paste turns quickly from white to a salmon or pink color. This method is stated to be sensitive to 0.02 mg of mercury. Evolution of alkaline vapors or hydrogen sulfide interfere with the sensitivity of the test. The interference due to alkaline vapors can be prevented by carefully placing a 2-mm layer of potassium pyrosulfate over the alkaline fusion mixture; interference due to sulfide can be avoided by using a 2-mm layer of litharge.

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CHAPTER 4

Classification by Solubility

THIS chapter deals with the classification of organic compounds on the basis of solubility tests and the elements found present in the compound. The determination of the solubility of organic compounds in selected solvents and the use of the solubility data in classifying such compounds for identification purposes have been a common practice for many years.[1] The scheme used in this chapter extends the former practice by classifying the compounds on the basis of the elements found present as well as on the solubility data. Such a method has the marked advantage of further restricting the number of possible chemical classes for which functional tests must be made in the final identification of a compound.

In order to show the relationship of solubility classifications to the whole problem of identifying an unknown organic compound, a summary of the necessary steps follows.

1. The elements present are determined. It is usual to assume that carbon and hydrogen are present in organic unknowns. If a residue results from ignition of the compound, it should be analyzed for the metals. These and other pertinent facts will be obtained from the tests made as described in Chapter 3.

2. On the basis of the elements present and on the solubilities as determined in this chapter, the unknown may be assigned to appropriate subclasses. To identify the compound, the search need no longer include the whole field of organic compounds, but may be restricted to, at most, a few functional classes or subclasses.

3. The functional groups present in the unknown are identified by the chemical reactions that the compound will undergo. Tests for these functional groups are given in Chapters 5 and 6. As a result of these tests, it is possible to classify the compound as belonging to a specific chemical class, or even to a subclass, such as: nitro acids, amino phenols or halogenated aromatic amines.

[1] Kamm, *Qualitative Organic Analysis*, 2nd Ed., John Wiley and Sons, Inc., New York, 1932; Shriner and Fuson, *Identification of Organic Compounds*, 2nd Ed., John Wiley and Sons, Inc., New York, 1940; Staudinger, *Anleitung zur organischen qualitativen Analyse*, Verlag von Julius Springer, Berlin, 1925.

4. One or more of the physical constants of the unknown should now be determined, and the search made in the tables for those members of the identified chemical class that have physical constants approximating those found for the unknown. It is, of course, important that the unknown be pure before its constants are determined. The field of possibilities as to the identity of the unknown has now been narrowed down to a few compounds. If the elements that are known to be present, and all other known facts about its physical properties and chemical constitution are kept in mind, further restrictions may usually be placed on its identity.

5. The final proof of the identity of the compound comes as the result of making one or more derivatives. This subject is covered by later chapters.

Relationships between solubility and molecular structure. Solubility depends on intermolecular forces exhibited by both the solvent molecules and the solute molecules. The purposes of this book preclude the necessity of a detailed discussion of the causes of solubility. For such discussions, the reader is referred to the literature[2] for such subjects as bonding forces, bonding energies, polarity, dipole moments, induction effect, association polymers, hydrogen-bonding, chelation, resonance and dispersion forces. There is considerable disagreement among chemists as to the relative importance of the various factors in causing solubility.

The causes of solubility may be considered under three heads: Physical, intermediate, and chemical. There are no sharp lines of demarcation separating these three types, and the cases discussed under each heading will often be arbitrary selections. Solubility requires definite attraction between the solute and solvent. The attracting forces may be either physical or chemical. Both kinds of forces may be effective simultaneously.

The diffusion of solute molecules into a solvent is a phenomenon resembling the evaporation of a liquid or the melting of a solid. Other things being equal, high boiling points or high melting points indicate either molecular association or strong intermolecular forces between the molecules. Either of these factors would interfere with the diffusion of

[2] Branch and Calvin, *The Theory of Organic Chemistry*, Prentice-Hall, Inc., New York, 1941; Gilman, *Organic Chemistry*, 2nd Ed., John Wiley and Sons, Inc., New York, 1943; Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, 1940; Hildebrand, *Solubility of Non-Electrolytes*, 2nd Ed., Reinhold Publishing Corporation, New York, 1936; Remick, *Electronic Interpretation of Organic Chemistry*, John Wiley and Sons, Inc., New York, 1943; Sidgwick, *The Electronic Theory of Valence*, Oxford University Press, London, 1929; Waters, *Physical Aspects of Organic Chemistry*, Geo. Routledge and Sons, London, 1937; Wheland, *The Theory of Resonance*, John Wiley and Sons, Inc., New York, 1944.

a solute in a solvent and would therefore lower the solubility. If two solids have approximately the same heats of fusion, the one with the lower melting point will be more soluble in any given solvent. Similarly, of two solids having approximately the same melting points, the one with the lower heat of fusion will have the greater solubility in any given solvent. The solvent power of a liquid is lessened by the association tendency existing among its own molecules.

Water and ether as solvents. Water and ethyl ether are both polar solvents if the classification is based on dipole moments. However, apparently as the result of two factors, these compounds differ widely in their solvent power on polar compounds. One difference between them is that water is highly associated; ether is not. This leads to an abnormally high dielectric constant for water (80), whereas the dielectric constant for ether is low (4.3). Accordingly, ionic substances are soluble in water but not in ether, whereas nonpolar compounds dissolve in ether because of its unassociated composition. The other difference between water and ether as solvents is that water can form hydrogen bonds through either the hydrogen or the oxygen atom, whereas ether has only the oxygen atom.

Since other factors besides polarity determine solubility, predictions cannot be made on this basis alone. Solubility predictions are more reliable when applied to liquid solutes than to solids. Polarity is due to an unsymmetrical charge distribution along the molecule. Hydrocarbons have such a symmetrical distribution of charges that they are not soluble in water, but they are soluble in ether. The substitution of a polar group for a hydrogen in the hydrocarbon produces a dipole in the molecule, and thus increases the solubility of the compound in water and tends to decrease its solubility in ether. In general, the higher the dipole moment of a polar molecule, the greater its solubility in water. This polarity effect may, however, be more than offset by other factors. For example, nitrobenzene has a higher dipole than either aniline or phenol, but it is not so soluble in water as either of them. The explanation seems to lie in the fact that aniline tends to gain a proton from a water molecule and phenol tends to donate a proton to a water molecule, whereas nitrobenzene fails to react appreciably with water. In the cases cited, the chemical causes of solubility outweigh the physical.

It should be noted that in the case of polar compounds, such as acids, the hydrocarbon radical part of the molecule remains fundamentally insoluble in water but soluble in ether. As long as the hydrocarbon radical is not too large in comparison with the actively polar part of the molecule, the compound will be soluble in water. When the hydrocarbon

radical becomes the predominant factor, the compound will cease to be soluble in water to any great extent. The hydrocarbons butane and decane are nonpolar and insoluble in water. If they are converted into the corresponding butanoic (butyric) and decanoic (capric) acids, dipoles exist. Since each has one carboxyl group, the dipoles will be of approximately the same magnitude and will have, therefore, about the same attraction for the water molecules. However, the hydrocarbon radicals in the two molecules differ considerably, one being a propyl radical, the other a nonyl radical. Butanoic acid is soluble in water, but decanoic acid is very sparingly soluble.

Whether compounds are classed as "soluble" or "insoluble" will depend on the arbitrary limits set. It is general practice to call a solute soluble in a solvent if it dissolves in the room-temperature solvent to the extent of 3 per cent. On this basis, it has been found that one polar group in a molecule will make it soluble in water if it contains up to four carbon atoms in "normal" chains, or up to five carbon atoms in "branched" chains. In general, molecules with normal chains have greater intermolecular attraction, as evidenced by high melting points and lower solubility, than the isomeric branched chain forms. For solubility purposes, the phenyl radical has approximately the value of a butyl radical. The above "rules" are very useful observations, but they should not be regarded as infallible truths. Naturally, the more polar groups there are in one molecule, the more carbon atoms there can be in the molecule for water-soluble compounds.

While isomerism within the hydrocarbon radical affects solubility, isomerism with respect to the location of the polar group within the molecule has much greater effect on solubility. The solubilities of the isomeric pentanols[3] in water illustrate both of these factors, as is shown in Table IV.

It will be noted that for the primary alcohols, isomerism within the alkyl radical changes the solubility about 50 per cent of the normal pentanol value, whereas shifting the hydroxyl group from the first to the second carbon atom in the normal chain more than doubles the solubility, and the 3-pentanol is even more soluble. Where the effects of both types of isomerism are combined, the solubility is much greater. The tertiary pentanol is more than five times as soluble in water as the normal primary pentanol. The inductive effect of the groups attached to the *alpha* carbon atom may be the most important factor in the solubility differences mentioned.

Solubility differences of isomers are also noticeable in the aromatic

[3] Ginnings and Baum, *J. Am. Chem. Soc.*, **59**, 1111, (1937).

compounds. For example, in the cases of the amino-, chloro- and nitro-substituted benzoic acids, the solubility decreases as the substituent is moved from the *ortho* to *meta* to *para* positions.

Ether is a slightly polar, unassociated solvent. Among the slightly ionized compounds, those that have only one polar group are soluble in ether.

TABLE IV

Solubility of the Pentanols in Water

HYDROCARBON	PRIMARY ALCOHOLS	SOLUBILITY*
n-pentane	1-pentanol	2.36
2-methyl butane	3-methyl-1-butanol	2.85
2-methyl butane	2-methyl-1-butanol	3.18
2, 2-dimethyl propane	2, 2-dimethyl-1-propanol	3.74
	SECONDARY ALCOHOLS	
n-pentane	2-pentanol	4.86
n-pentane	3-pentanol	5.61
2-methyl butane	3-methyl-2-butanol	6.07
	TERTIARY ALCOHOL	
2-methyl butane	2-methyl-2-butanol	12.15

* Solubility is expressed in g/100g water at 20°.

Because of their high polarity, salts and sulfonic acids are not soluble in ether. A large majority of the compounds that are not soluble in water are soluble in ether, unless their solubility is inhibited by too great a polarity, or unless they are too highly associated. As in the case of water as the solvent, solubility in ether sometimes differs materially among isomers of the same compound.

Commercial ether contains small percentages of alcohol and water. These components increase the observed solubility above expectations for water-soluble and alcohol-soluble compounds that are sparingly soluble in ether. In the process of extracting a solute from water by ether or from ether by water, the two phases are actually not water and ether, but a saturated solution of ether in water and a saturated solution of water in ether. In terms of the arbitrary standards adopted for calling a compound "soluble," ether is soluble in water and water is soluble in ether. If benzoic acid is extracted from water by ether, much less of the acid will be recovered than is called for by the distribution law based on the solubility of benzoic acid in pure water and in pure ether. The acid is much more soluble in a saturated solution of ether in water than it is

in pure water, and less soluble in a saturated solution of water in ether than it is in pure ether.

Types of solutions: 1. *Physical solutions.* Solutions may be considered as being caused by physical forces rather than by chemical forces if: (1) they approximately obey Raoult's law; or (2) the solute and solvent are attracted to each other by forces between dipoles. The first of these classes is sometimes called *regular solutions.* Since this class calls for solutes and solvents that lack polarity, associating tendencies, solvating power, and solute-solvent reactivity, most of the solutions in benzene and carbon tetrachloride will come under this classification.

2. *Intermediate solutions.* As pointed out previously, the phenomenon of dissolving a solute is complex. Often several types of physical forces and chemical forces[4] are playing their independent roles of inducing solubility, or of retarding it. Between the extremes of purely physical dispersion of the solute into the solvent on the one hand, and the cases of definite chemical reactions, like the conversion of a water-insoluble acid into a water-soluble salt in aqueous sodium hydroxide, on the other, there is a variety of intermediate causes of solubility. Many of these causes may be classified under the heading of solvation, several types of which are discussed below.

a. *Hydrogen-bonding.* The hydrogen-bond results from the mutual attraction of two electronegative atoms for a proton. Only F, O, N and Cl can form hydrogen-bonds, and their activity decreases in the order listed. Nonelectrolytes generally do not dissolve in water unless they can form hydrogen-bonds with the water molecules. The solubility of a compound in water depends on the number of hydrogen-bondable groups in the molecules and on the magnitude of the hydrocarbon part of the molecule. The effect of hydrogen-bonding on solubility in water may be well illustrated by the following facts: the hydrocarbons ethane and benzene, together with their halogen substitution products, are all very slightly soluble in water, whereas the hydroxy or amino substitution products of these hydrocarbons are much more soluble. The hydrogen-bond is a weak bond as compared with the covalent hydrogen-bond. The hydrogen-bond has a strength of about 5 kilocalories as compared with the covalent H—O bond with 110 kilocalories, or the co-valent H—H bond with 103 kilocalories.

With solvents other than water, particularly the alcohols and, on occasion, chloroform, hydrogen-bonding causes solubility. Chloroform will dissolve many compounds that are not soluble in carbon tetra-

[4] Hildebrand, *Science*, **83**, 21, (1936).

chloride. It should be noted that these compounds contain active *donor groups* for hydrogen-bond formation.

Special cases of hydrogen-bonding are discussed under separate headings in the paragraphs that follow.

b. *Chelation.* When hydrogen-bondable groups are situated in resonating molecules in such positions that hydrogen-bond formation may occur, a cyclic structure is formed. This process is called *chelation.* A few cases will illustrate the effect of chelation on solubility and on the expected chemical tests for the compounds under consideration. It has long been known that when such donor groups as —HC=O, or $—NO_2$ are located *ortho* to the —OH group in a phenol, the compounds behave abnormally with respect to solubility and chemical reactions. What is true of the phenols seems to be true for the primary arylamines and hydrazines. The chelated forms of salicylaldehyde and *o*-nitrophenol may be written as:

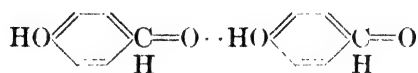
```
 —O—H          —O—H
    :             :
 —C=O          —N—O
  |              ||
  H              O
```

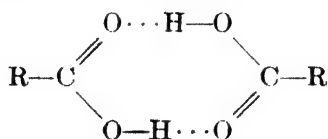
Such structures inactivate the —OH group as regards hydrogen-bondability with water, salt formation with sodium hydroxide solutions or other characteristic reactions of the phenolic group. They also prevent the formation of association polymers among the molecules of the compound itself. These statements are sustained by laboratory experience.

c. *Association polymers.* The tendency of the molecules of many compounds to associate together as polymers is another illustration of hydrogen-bonding. It has a marked influence on solubility. If the molecules of the solvent associate, the possibility for a solute to diffuse into that solvent is decreased. Also, if the solute tends to form hydrogen-bonded attachments to the solvent, that process is interfered with by the fact of solvent association. Water and the low molecular weight alcohols are highly associated solvents. Ether, benzene, carbon tetrachloride and chloroform are nonassociated solvents.

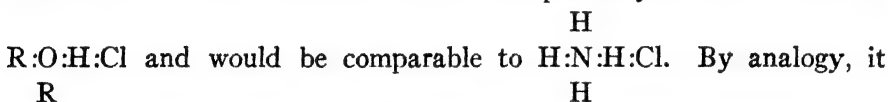
Association of the solute molecules with each other also decreases the solubility in those solvents having acceptor hydrogen atoms, such as water and the alcohols. However, association may increase the solubility in ether by decreasing the number of actively polar groups present in any one molecule. As pointed out previously, chelated molecules do not form association polymers and hence the molecular weight remains

normal for the compound. Therefore, two reasons why salicylaldehyde is more soluble in ether than the isomeric *p*-hydroxybenzaldehyde are that: (1) it has no actively polar group; and (2) it has a lower molecular weight. In spite of its association, the un-chelated *para* isomer is more soluble in water than the chelated *ortho* compound because it still has some active hydrogen-bonding groups on the "ends" of the polymer—*e.g.*, in the dimer:

```
HO<ring>C=O··HO<ring>C=O
         H              H
```

Many acids form association polymers of the type:

```
        O···H—O
       //      \
R—C              C—R
       \      //
        O—H···O
```

Such association interferes with solubility in water and in alkaline solutions. Association, like chelation, interferes with chemical tests for specific groups that are involved. Since these forms are in equilibrium with other isomeric forms of the molecule, the tests are usually merely retarded, not prevented.

d. *Oxonium compounds.* Compounds like methyl ether hydrochloride are known. Such a molecule would probably have the structure:

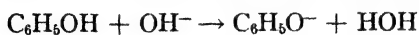
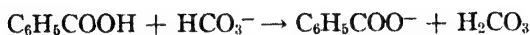
```
                                                  H
R:O:H:Cl and would be comparable to H:N:H:Cl. By analogy, it
  R                                               H
```

would be called an oxonium salt. Some writers designate the H_3O^+ ion, the *oxonium ion*, owing to analogy with the NH_4^+ ion. Since ethers dissolve in concentrated sulfuric acid, but separate out if the acid is diluted, it seems probable that the ethers react with the acid to form oxonium salts. Perhaps the solubility of aldehydes, ketones and esters in concentrated sulfuric acid is explainable on the same basis.

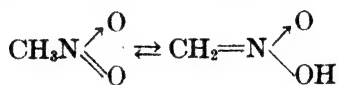
3. *Chemical solutions.* When the solubility is caused by a reaction between the solute and the solvent, or ions present in the solvent, for which an equation would ordinarily be written, it is classed as a chemical solution. For example, the unsaturated noncyclic hydrocarbons dissolve in concentrated sulfuric acid because they react with it to form alkyl sulfuric acids. Similarly, the alcohols dissolve in concentrated sulfuric acid because of a dehydration reaction to form the alkyl sulfuric acids or the dialkyl sulfates in addition to their tendency to form oxonium compounds. The two major types of compounds of interest in classify-

ing an unknown on the basis of chemical solubility are the water-insoluble compounds that dissolve in dilute acid solution and those that dissolve in basic solutions.

a. *Solubility caused by bases.* The bases used in aqueous solution to classify acids by solubility are the bicarbonate and the hydroxyl ions. As a result of the reaction of the molecular acid with the base, an organic anion base will be formed together with carbonic acid or water. For example:

$$C_6H_5COOH + HCO_3^- \rightarrow C_6H_5COO^- + H_2CO_3$$

$$C_6H_5OH + OH^- \rightarrow C_6H_5O^- + HOH$$

Sodium bicarbonate and sodium hydroxide are used to supply the bicarbonate and hydroxyl ions; hence sodium ions will be present in the solutions. The hydroxyl ion is a stronger base than the bicarbonate; hence the acids that will dissolve in a solution of sodium hydroxide may be less highly ionized than those that will dissolve in a solution of sodium bicarbonate. As was explained under the discussion of physical solutions, the polar salts are soluble in water. The dissolving of a molecular acid in a solution of sodium hydroxide involves the chemical conversion of the acid to an ion, and then the formation of a physical solution of the ion in the water. The water-insoluble *carboxylic acids*, *sulfonic acids*, *sulfinic acids*, and the more *negatively substituted phenols* are soluble in a solution of sodium bicarbonate, *as well as* in a solution of sodium hydroxide. The other phenols, thiophenols, aryl sulfonamides of primary amines, some enols, some imides, oximes, primary and secondary nitroparaffins and N-substituted hydroxylamines are soluble in sodium hydroxide solution but *not* in a solution of sodium bicarbonate. Compounds are soluble in a sodium hydroxide solution if they contain the =N—OH group. This explains the solubility of the nitroparaffins, where the *aci* isomer contains the =N—OH group:

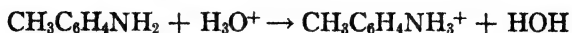
$$CH_3N\begin{smallmatrix}\nearrow O \\ \searrow O\end{smallmatrix} \rightleftarrows CH_2{=}N\begin{smallmatrix}\nearrow O \\ \searrow OH\end{smallmatrix}$$

Some *p*-nitroso phenols have an *aci* isomer which is an oxime. Hence, they dissolve in sodium hydroxide solutions.

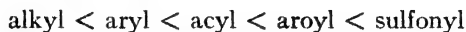
b. *Solubility of amines.* When water is the solvent, amines owe their solubility to their tendency to form ions by combining with a hydrogen ion from the water. Thus, for a tertiary amine, the equation would be:

$$R_3N + HOH \rightleftarrows R_3N{:}HOH \rightleftarrows R_3N{:}H^+ + OH^-$$

When the substituent groups in the original NH_3 are of such nature or

magnitude as to render the amine insoluble in water alone, the amine may dissolve in dilute acids because of the greater availability of hydrogen ions in acidic solutions.

$$CH_3C_6H_4NH_2 + H_3O^+ \rightarrow CH_3C_6H_4NH_3^+ + HOH$$

c. *Summary of substituted ammonias.* The order of electronegativity—that is, the electron-attracting power—of groups that may be substituted for hydrogen in ammonia is:

$$\text{alkyl} < \text{aryl} < \text{acyl} < \text{aroyl} < \text{sulfonyl}$$

The alkyl radical has about the same electronegativity as the hydrogen atom. Therefore, molecules of the types RNH_2, R_2NH and R_3N have about the same basicity as NH_3 itself. In aqueous solutions, the ionization constant for such compounds is of the order of 10^{-3} to 10^{-5}. For example, for methyl amine the $K_b = 5 \times 10^{-4}$.

$$\frac{[CH_3NH_3^+] \times [OH^-]}{[CH_3NH_2]} = K_b = 5 \times 10^{-4}$$

The aryl radical is much more electronegative than the alkyl radical. Therefore, the $ArNH_2$ amines are much less basic than the alkylamines. They have ionization constants of the order of 10^{-10}. For example, the K_b for aniline is 3.8×10^{-10}.

$$\frac{[C_6H_5NH_3^+] \times [OH^-]}{[C_6H_5NH_2]} = K_b = 3.8 \times 10^{-10}$$

The ArNHR and $ArNR_2$ amines have about the same basicity as the $ArNH_2$ amines. The substitution of electronegative groups for hydrogen in the aryl radical would, of course, decrease the basicity of the arylamines.

Association or chelation is possible in some of the nitro-substituted arylamines, and decreases their basicity.

An interesting case of differences in solubility among isomers of different structure is shown by benzylamine and the toluidines. Benzylamine is really phenylmethylamine and acts like an alkylamine. In spite of the presence of the phenyl radical and a fairly high molecular weight, it is completely soluble in water. The toluidines, which are methylanilines, are much less soluble in water than aniline itself. Benzylamine does not *resonate* but the toluidines do. Resonating systems reduce the basicity by removing electrons from the nitrogen atom. Alkyl groups supply an induced negative charge to the nitrogen and thus make the basicity greater.

The substitution of two aryl radicals for hydrogen in ammonia reduces

the basicity practically to neutrality. The $(Ar)_2NH$ and $(Ar)_2NR$ amines, as well as the negatively substituted $ArNH_2$ amines mentioned above, fail to dissolve in a 6 *N* solution of hydrochloric acid. The $(Ar)_3N$ amines are neutral.

One acyl radical is about equal in electronegative effect to three aryl groups. The aliphatic amides, like the triarylamines, are neutral. The aromatic amides are very slightly acidic. The sulfonamides are definitely acidic. The imides, which have two acyl or aroyl groups substituted for hydrogen in ammonia, are acidic. The most common imides are those formed from dibasic acids.

The N-substituted amides are a "mixed" type, having either acyl, or aroyl groups and alkyl or aryl groups substituted for hydrogen in ammonia. In terms of the electronegativity of the groups present, molecules of this class are neutral or acidic, depending on the nature of the specific groups present. The molecules of $RCONH_2$ and RCONHR are probably *associated*, as they have higher melting points and lower solubility than the $RCONR_2$ compounds.

Intermediate Bases:
RNH_2, R_2NH, R_3N, $ArCH_2NH_2$. Generally soluble in water and ether. Soluble in hydrochloric acid, if water-insoluble.

Weak Bases:
$ArNH_2$, ArNHR, $ArNR_2$, $RCONR_2$. Generally insoluble in water, soluble in hydrochloric acid.

Practically Neutral:
$(Ar)_2NH$, $(Ar)_2NR$, $(Ar)_3N$, $RCONH_2$, RCONHR, $ArCONH_2$. Generally insoluble in water and in hydrochloric acid.

Weak Acids:
ArNHR, $(RCO)_2NH$, ArCONHR, RSO_2NH_2, RSO_2NHR, $ArSO_2NH_2$, $ArSO_2NHR$. Some of these compounds are soluble in water. The solubility in sodium hydroxide increases with the electronegativity of the attached groups.

d. *Amphoteric compounds.* The amphoteric molecules contain groups capable of reaction with either acids or bases. Many of them are soluble in water, and those that are not are generally soluble in both acidic and alkaline solutions. In the classifying tests, if a water-insoluble compound is found to be soluble in hydrochloric acid, it should also be tested for solubility in sodium hydroxide to detect any amphoteric property.

The most common class of amphoteric compounds is the amino acids. The water-insoluble members of the aliphatic amino acid class are soluble in both hydrochloric acid and sodium hydroxide solutions if the

—NH_2 group is un-substituted, or has only alkyl substituents. The amino aromatic acids are generally soluble in hydrochloric acid and sodium bicarbonate solution. The N-diaryl amino acids, such as diphenylamino acetic acid, are not soluble in acid, but, if water-insoluble, are dissolved by sodium bicarbonate solution.

Some other amphoteric classes are the numerous amino phenols, the amino thiophenols and the amino sulfonamides. The amphoteric compounds exist in aqueous solution as the dipolar ions—*e.g.*, $^{+}H_3NC_6H_4O^{-}$.

Solubility determinations. For the purposes of this text, a compound is considered soluble in a solvent if 30 mg of it dissolve in 1 ml of the solvent at room temperature. In doubtful cases, the mixture should be shaken for 2 minutes before a decision is reached as to whether or not the compound has dissolved. In case the compound being tested is a liquid, 1 drop of the compound in 15 drops of the solvent is a good approximation of the proper quantities. The use of a narrow, 3-inch test tube is recommended for the solubility determinations.

The solvents to be used for the solubility classifications are, in the order in which they should be used: **water, ether,** 10 per cent aqueous **hydrochloric acid,** 10 per cent aqueous **sodium hydroxide,** 10 per cent aqueous **sodium bicarbonate** and **concentrated sulfuric acid.** All solubilities are to be determined at room temperature. It is permissible to warm the mixture slightly during the test but the mixture should be cooled before a decision is reached as to its solubility. Less concentrated solutions, e.g., 4–5 per cent, of hydrochloric acid, sodium hydroxide and sodium bicarbonate, may be used but the reaction rates are frequently quite slow.

It is not necessary to test every compound in all of the solvents; rather, the solvent should be used in the order listed above and the first solubility class found should be accepted. If the compound is soluble in water, its solubility may be tested in ether, but not in any other solvent. If the compound is not soluble in water, there is no need to test it with ether. Water-insoluble compounds that are soluble in hydrochloric acid should also be tested with sodium hydroxide to detect amphoteric compounds. Substances that are insoluble in water but soluble in sodium hydroxide should also be tested with sodium bicarbonate to distinguish between relatively strong acids and the weakly acidic compounds. If an obvious chemical reaction occurs in any solvent, the compound may be considered as soluble in that solvent. A few of the amine hydrochlorides are sparingly soluble in 10 per cent hydrochloric acid; hence in these cases the original amine will react when first added to the aqueous acid to form the amine hydrochloride and then precipitate as

that salt. To determine whether the insoluble material is the original amine or a salt that has been formed, a mixed-melting-point determination should be made, using the *washed and dried* solid from the acid solution with some of the original sample.

In making the solubility tests, the elements that were found present in the compound should be borne in mind. Unless nitrogen is present, there is no need to test for solubility in hydrochloric acid. If the compound contains nitrogen or sulfur and is insoluble in water, hydrochloric acid and sodium hydroxide, it is arbitrarily placed in a special "miscellaneous" division without testing its solubility in concentrated sulfuric acid.

Designation for the solubility divisions. Letters that relate to the solvents used to classify the unknown are used to designate the Solubility Divisions. The letters are **W** for water, **E** for ether, **H** for Hydrochloric acid, **A** for alkali, **C** for carbonate, **M** for miscellaneous, **S** for sulfuric acid and **I** for insoluble.

Division W. This division includes the compounds that are soluble in water but insoluble in ether.

Division E. This division includes the compounds that are soluble in both water and ether. Very few compounds that contain two or more of the elements nitrogen, halogens or sulfur fall in this division.

Division H. Compounds that are insoluble in water but soluble in 10 per cent hydrochloric acid belong in this division. They all contain nitrogen. Not all the amines will dissolve in dilute acid, however, and many of them fall in the miscellaneous division.

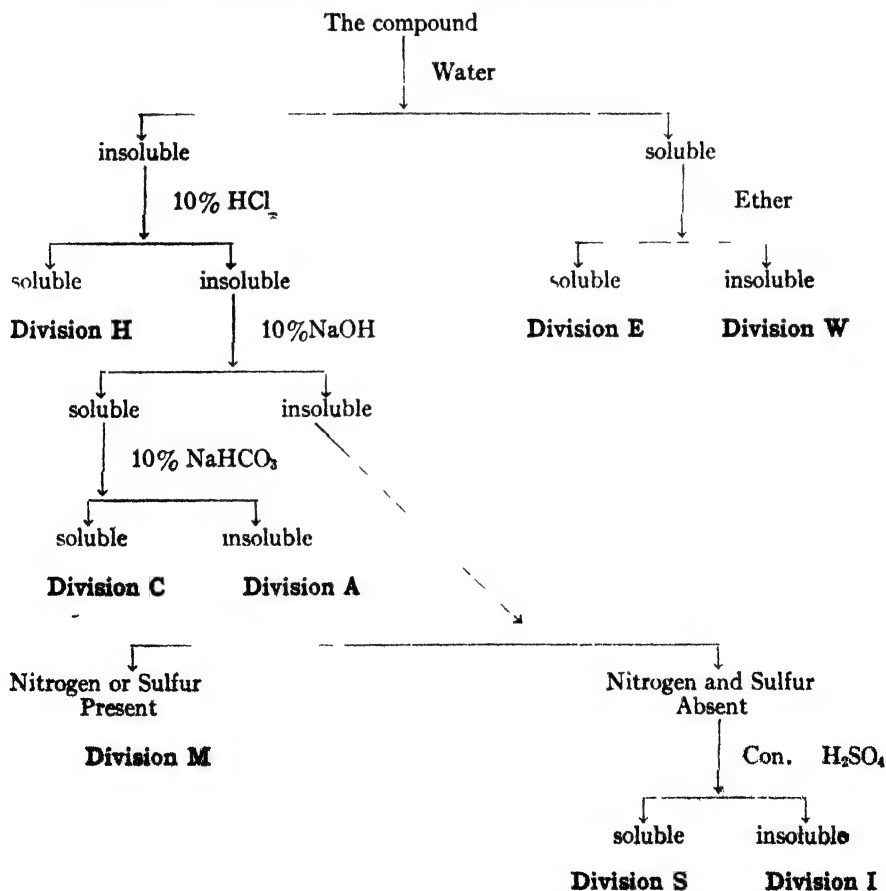
Division A. This division includes the compounds that are insoluble in water and insoluble in a 10 per cent sodium bicarbonate solution, but which are soluble in a 10 per cent sodium hydroxide solution.

Division C. The compounds in this division are insoluble in water but soluble in both 10 per cent sodium bicarbonate solution and 10 per cent sodium hydroxide solution.

Division M. Compounds that contain nitrogen or sulfur, and which have been found insoluble in all of the solvents used thus far, are placed in this miscellaneous division. The list of compounds that fall in this division is very long. Only the most common chemical classes are included in the solubility tables of this chapter. Halogens may, of course, be present in the compounds of this division.

Division S. Compounds that are soluble in concentrated sulfuric acid but are insoluble in the other solvents used belong in this division. Nitrogen and sulfur are both absent since their presence would classify the compound in Division **M**. Compounds containing halogens are not

common in this division but there are exceptions, such as chloracetophenone and halogenated hydrocarbons in which the halogen is in the side-chain and the aromatic part of the molecule is easily sulfonated. Some aromatic hydrocarbons fall in this division because they are easily sulfonated.

Division I. Compounds that are insoluble in all the classification solvents and do not contain nitrogen or sulfur belong in this division.

DIVISIONAL SOLUBILITY CLASSIFICATIONS

Division W[a] [b]

a. Only C, H and O present

DIBASIC AND POLYBASIC ACIDS
HYDROXY ACIDS
POLYHYDROXY PHENOLS
Simple carbohydrates

b. Metals present

SALTS OF ACIDS AND PHENOLS
Miscellaneous metallic compounds

c. Nitrogen present

AMMONIUM SALTS
AMINE SALTS OF ORGANIC ACIDS
AMINO ACIDS
Amides
Amines
Amino phenols
Nitro acids
Nitro phenols
Semicarbazides
Semicarbazones
Ureas

d. Halogen present

HALO ACIDS
Halo alcohols, aldehydes, etc.
Acyl halides (by hydrolysis)

e. Sulfur present

SULFONIC ACIDS
Mercaptans

f. Nitrogen and halogen present

Amine salts of halogen acids

g. Nitrogen and sulfur present

AMINO SULFONIC ACIDS
BISULFATES OF WEAK BASES
Cyano sulfonic acids
Nitro sulfonic acids

Division E

a. Only C, H and O present

CARBOXYLIC ACIDS
ALCOHOLS
ALDEHYDES AND KETONES
Anhydrides
Esters
Ethers
Polyhydroxy phenols

b. Nitrogen present

AMIDES
AMINES
Amino acids and phenols
Nitro acids and phenols

c. Halogen present

Halo acids and phenols

d. Sulfur present

Hydroxy heterocyclic sulfur compounds
Mercaptans
Thiophenols

Division H

AMINES[c]
Amino acids
Aryl substituted hydrazines
N-dialkyl amides
Amphoteric compounds

Division C

a. Only C, H and O present

ACIDS AND ANHYDRIDES

b. Nitrogen present

AMINO AROMATIC ACIDS
NITRO ACIDS
Cyano acids
Polynitro phenols

c. Halogens present

HALO ACIDS
Polyhalo phenols

[a] Nitrogen, halogens and sulfur are absent unless specified
[b] In this table, the more common classes are printed in small capital letters.
[c] Mainly the primary arylamines. Amines with strong negative substituents fall in Division *M*.

d. Sulfur present
- SULFONIC ACIDS
- Sulfinic acids
- Mercaptans

e. Nitrogen and sulfur present
- Nitro thiophenols
- Sulfates of weak bases
- Sulfonamides

f. Sulfur and halogens present
- SULFONHALIDES

Division A

a. Only C, H and O present
- PHENOLS
- Enols

b. Nitrogen present
- AMINO ACIDS[d]
- NITRO PHENOLS
- Amides[e]
- Amino phenols
- Cyano phenols
- N-monoalkyl aromatic amines
- N-substituted hydroxylamines
- *p*- and *s*- Nitroparaffins
- Trinitro aromatic hydrocarbons
- Oximes
- Ureides

c. Halogens present
- HALO PHENOLS

d. Sulfur present
- Mercaptans
- Thiophenols

e. Nitrogen and halogen present
- Polynitro halogenated aromatic hydrocarbons
- Substituted phenols

f. Nitrogen and sulfur present
- Alkyl sulfonamides
- Aryl sulfonamides
- Amino thiophenols
- Amino sulfonic acids
- Thioamides

Division M[f]

a. Nitrogen present
- ANILIDES AND TOLUIDIDES
- AMIDES
- NITRO ARYLAMINES
- NITRO HYDROCARBONS
- Diarylamines
- Azo-, hydrazo-, and azoxy-compounds
- Dinitro phenylhydrazines
- Nitriles
- Amino phenols

b. Sulfur present
- Sulfides
- Sulfones
- N-dialkyl sulfonamides
- Thio esters
- Thiourea derivatives

Division S

- ALCOHOLS
- ALDEHYDES AND KETONES
- ESTERS
- ETHERS
- UNSATURATED HYDROCARBONS[g]
- Anhydrides

Division I

- HYDROCARBONS[h]
- Halogen derivatives of hydrocarbons

[d] Mainly of the aliphatic series.
[e] Including N-monoalkyl amides.
[f] Only the most common classes are listed.
[g] All noncyclic unsaturated hydrocarbons, and those unsaturated cyclics that are easily sulfonated.
[h] Including most of the cyclic hydrocarbons, and all of the saturated, noncyclic hydrocarbons.

CHAPTER 5

Charting the Experimental Course

IN ORDER that further work may be undertaken in proper sequence, an inventory should now be made of all the facts that have been learned about the compound under examination.

The tests in Chapter 3 showed how to determine the presence or absence of salts, active unsaturation, the probable cyclic structure and the elements present in the purified compound. A list of the known properties should now be made, and they should be taken into consideration in conjunction with the data on elements present and the probable Solubility Division for the compound (Chapter 4). Unless the presence of polyfunctional groups has interfered too much with the tests that have been made, it is now possible to assign the unknown to one of a restricted number of chemical classes. The possible classes should be listed on the basis of all the facts at hand.

The selection of a logical order of procedure. To decide definitely to which of the foregoing classes the compound belongs, the identity of the functional groups present is first determined. The next step, then, is to decide the order in which the tests are to be made, so that as few as possible will be required to identify the compound.

The reader's general knowledge of organic chemistry will be of great help. Some suggestions that may prove useful follow:

1. A test or observation that eliminates a class is significant.
2. It is logical to suspect a class that is commonly used in laboratories or industry before considering an uncommon one.
3. If the compound is even slightly soluble in water, the *p*H of the solution is an important clue.
4. The great majority of carbon compounds are colorless. Therefore, if the pure compound is colored, certain groups may be suspected, and the selection of further tests to be applied would take those facts into account. While the exact cause of color in molecules is still somewhat uncertain, several authors have logically summarized the present theories on the subject.[1] Among compounds containing carbon, hydrogen, oxygen, halogens or sulfur, there are a few colored substances, mainly

[1] E.g., Remick, *Electronic Interpretations of Organic Chemistry*, John Wiley and Sons, Inc., New York, 1943.

quinones, *aromatic ketones* that have unsaturated side-chains and a very few *alkanediones*.

If nitrogen is present, with or without the additional presence of halogens or sulfur, the most common colored compounds are substituted anilines, toluidines, polycyclic amines or hydrazines; nitro, nitroso or amino phenols; polynitro or polyamino hydrocarbons; nitro or amino quinones; azo or diazo compounds; picrates; hydrazones or osazones. Aside from the azo compounds, which are generally orange or red, compounds that contain only chromophoric groups, such as —N=N—, =C=S, =C=O, —N=O, $—NO_2$ and the *o*- or *p*- quinoid structures are usually yellow. If, however, the compound also contains auxochromic groups, such as $—NH_2$, —NHR, —OH or —SH, the color is deepened and intensified. Some of the halogenated nitrohydrocarbons are colored. The color tends to deepen as the halogen is changed from chlorine to bromine and from bromine to iodine.

Unsubstituted anilides are colorless. Many compounds tend to darken on exposure to light or air, and hence a purified sample should always be used for color estimation.

5. When one is considering the probable class of a compound on the basis of the elements present, the most probable combinations should be considered first; e.g., if sulfur is present, but no nitrogen, sulphonic acids would be the most likely, whereas, if both sulfur and nitrogen were present, sulphonamides would be most likely. If both chlorine and nitrogen were present, the compound might belong to any one of several classes, but the most probable combinations would be chloroanilines or amine hydrochlorides.

By a judicious use of the classification made on the basis of both the solubility and the elements found present in an unknown, a logical selection of further tests may be made. Most of the classification tests for functional groups are given in the next chapter. If the compound falls in Solubility Divison **H**, the tests applicable to amines should be tried at once. Compounds in Solubility Division **A** or **C** should be tested for acids, phenols and anhydrides. Division **M** compounds present more difficulty, since this division includes the less reactive subclasses of nitrogen or sulfur-containing compounds, and the reader will have to consider many tests with no really logical order of selection possible. If the Division **M** compound under examination contains nitrogen, the first test that should be run is the diazo test for primary aromatic amines, since many of the substituted amines, particularly if the substituents are in the *ortho* or *para* positions, fail to dissolve in the dilute hydrochloric acid of Division **H**. Many cyclic amides and anilides also fall in Divi-

sion **M**. Division **I** compounds should be examined for hydrocarbons and halides.

The reader should prepare a list of the tests to be made, in the order of their probable usefulness in determining the class to which the unknown belongs.

Preliminary classification tests. The tests given in this chapter are preliminary general tests that may be used to identify quickly certain general types of compounds. There is considerable duplication of classes or compounds in the Solubility Divisions **W**, **E**, and **S**, and hence, to some extent, the same systematic approach to the tests may be made. If the compound is in Division **W**, it may be any one of four types of compounds that could not also fall in Divisions **E** or **S**—namely: carbohydrates, acyl halides, acid salts of amines and metallic salts of organic compounds. In the following tests, numbers 5.1 to 5.4 should identify these types.

The acidity, neutrality or alkalinity of a water solution of a compound should always be determined. This information is obviously useful in determining the class of compound that might be present. Test 5.5 gives the method that may be used in determining the *p*H of aqueous solutions.

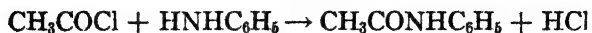
Since the hydroxyl group is present in several classes of compounds, including polyfunctional substances, several methods are given in Test 5.6 for identifying the hydroxyl group. More specific tests for the various classes of compounds containing the hydroxyl group are given in Chapter 6.

5.1 Molisch test for carbohydrates. The pentoses and their anhydrides are decomposed by concentrated sulfuric acid to form furfural. The hexoses and their anhydrides analogously produce hydroxymethylfurfural. These furfurals produce colored condensation products with α-naphthol, the composition of which is not known.

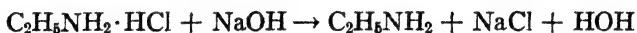
Dissolve about 50 mg of the suspected carbohydrate in 1 ml of water and add 2 drops of a 5 per cent solution of α-naphthol in alcohol. Place 1 ml of concentrated sulfuric acid in a 4-inch test tube clamped to a stand at an angle of about 45°. By means of a pipette, slowly introduce the solution to be tested so that it stratifies on top of the acid. A violet-purple color will develop at the interface of the two layers if the compound is a carbohydrate. If the test is positive, proceed with the tests for specific carbohydrates that are presented in the next chapter.

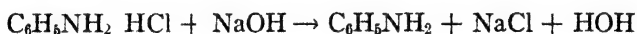
5.2 Test for acyl or aroyl halides. The acyl and aroyl halides react with primary and secondary amines to form substituted amides. If aniline is used as the amine, the product is called an anilide rather than

an N-substituted amide. The anilides are not soluble in cold water and can be used to detect acyl or aroyl halides.

$$CH_3COCl + HNHC_6H_5 \rightarrow CH_3CONHC_6H_5 + HCl$$

Place 0.1 ml (2 drops) of aniline in a 4–6 inch test tube and cautiously add 1 drop of the acid halide. If no reaction occurs, warm the mixture very slightly; add 3 ml of water and shake the tube vigorously. If the compound is an acyl or aroyl halide, a precipitate of the anilide will form.

5.3 Test for an amine salt. The amines form hydrogen-bonded complex salts with acids. These salts may be easily decomposed by adding sodium hydroxide, thus producing the free amine. Many of the alkylamines are soluble in water, but their formation may be easily detected by the odor and alkalinity of the vapors of a hot mixture of the amine salt and sodium hydroxide.

$$C_2H_5NH_2 \cdot HCl + NaOH \rightarrow C_2H_5NH_2 + NaCl + HOH$$

Many of the amines are water-insoluble liquids, and their formation may be detected by the separation of a second liquid phase. They can be extracted by ether.

$$C_6H_5NH_2\ HCl + NaOH \rightarrow C_6H_5NH_2 + NaCl + HOH$$

In case the free amine is a solid, there may be doubt as to whether or not a reaction with the sodium hydroxide has occurred. This point may be settled by testing the solubility of the substance in ether. An amine salt is not soluble in ether, whereas the free amine is soluble in ether.

Add 100 mg of the suspected amine salt to 3 ml of 10 per cent sodium hydroxide solution. If no reaction is apparent, warm the mixture to see whether an amine is liberated. The low-molecular-weight amines are gases with fishy odors; the higher amines are insoluble oils that are less dense than water.

5.4 Metallic salts. If the fusion test indicated the presence of metals in the compound, the metal should be identified by the usual inorganic analysis. The majority of such metallic compounds are salts of acids, phenols or oximes, although some other classes such as mercaptides and xanthates are possible. The compound should be freed of the metal, generally by careful acidification, and the organic part of the molecule identified by a systematic procedure.

5.5 pH test: a. *Single-indicator method.* Compounds that are soluble in water may be tested directly with either indicator solutions or test papers. Compounds that are sparingly soluble in water may be satisfactorily tested by moistening the test paper with distilled water and

then placing a drop of the liquid, or a pulverized sample of the solid, directly on the paper. If a solid is used, scrape the solid from the paper after a few minutes to examine the effect. While litmus is often useful, Congo Red is recommended for acidic compounds, and Thymol Blue or phenolphthalein for basic substances. The above indicators will only detect the moderately strong acidic or basic compounds.

Impurities. Many compounds may contain small concentrations of strongly acidic impurities, in which case false conclusions may be drawn from the acidity test. To determine whether the observed acidity is due to the compound itself or to an impurity, dissolve a 0.1-ml (or 50-mg) sample in 2 ml of distilled water and test it by dropwise titration with a 2.5 per cent solution of sodium hydroxide, using phenolphthalein as the indicator. One drop of the alkali will be sufficient for a nonacid, but more than a milliliter of the alkali will be required for really acidic compounds. If a few drops only are required, it may be assumed that the observed acidity was due to impurities—*e.g.*, acetic acid in acetaldehyde

b. *Mixed-indicator method.* Several commercially prepared mixtures of indicators are available,[2] both in solution and as test papers. These indicator mixtures show various colors that indicate within one *p*H unit the acidity or alkalinity of the solution. The use of such mixed indicators is recommended for approximation purposes.

The use of four mixed-indicator solutions has been proposed[3] for classifying organic compounds into the following classes: strong acids, intermediate acids, weak acids, ampholytes, neutral compounds, weak bases and intermediate bases. Experience has shown that if these indicator mixtures are made up with considerable care, the method is extremely valuable. It is much more satisfactory for determining proper classification of the weak acids, ampholytes and weak bases than is the simple solubility method using dilute acid and dilute base solvents. It is true, however, that the solubility method will properly classify the great majority of compounds. Those who desire to use the multiple-indicator method should consult the original articles, because the details given for the preparation of the indicators must be followed exactly. The articles contain a good discussion of the theory and results of the tests.

5.6 Tests for hydroxy compounds. Alcohols, phenols, hydroxy acids, hydroxy carbonyl compounds and a few other classes all contain the hydroxyl group. Acids and carbohydrates also contain the hydroxyl group, but, except where noted, these two classes do not give the tests below. If the compound is found to contain the hydroxyl group, the

[2] See the Appendix, page 462.
[3] Davidson, *J. Chem. Educ.*, **19**, 154, 221, and 532 (1942).

tests in the next chapter should be used to distinguish the specific class.

a. *Molybdic acid test.* Mild reducing agents, including hydroxy compounds, act upon an excess of molybdic acid to produce a blue precipitate that appears to be a molybdenyl molybdate, $(MoO)_3(MoO_4)_2$ or $(MoO_2)_2MoO_4$. Probably these compounds are responsible for the color in the following test.

Dissolve or suspend the compound in 1 ml of water and pour it down the side of a 3-inch test tube containing 1 ml of the molybdic acid reagent, so that the liquids stratify. A blue-violet ring forms at the interface if the compound contains a hydroxyl group. The test is not satisfactory unless the compound is reasonably soluble in water. Let the mixture stand for 5 minutes before making a final decision. Some amines give a green-colored ring. The reagent should be used within a few days after preparation for best results.

b. *Ceric nitrate test.* It has been found[4] that alcohols, glycols, hydroxy acids, hydroxy esters and hydroxy aldehydes or ketones containing 10 or less carbon atoms produce a red coloration when treated with the *ceric nitrate reagent. Phenols give conflicting colors. Aromatic amines as well as compounds containing chromophoric groups interfere by giving colors or precipitates with the reagent.* If "ROH" is used to represent the hydroxy compound, the equation for the color-forming reaction may be written as:

$$Ce(NO_3)_6^{=} + ROH + HOH \rightarrow Ce(OR)(NO_3)_5^{=} + H_3O^+ + NO_3^-$$

Dissolve 50 mg (or 1 drop) of the compound to be examined in 0.5 ml of water or dioxane. In a separate tube add 0.5 ml of a *freshly prepared* ceric nitrate reagent (see Appendix, page 462) to 3 ml of the same solvent. Now add 2–5 drops of the solution to be tested to the reagent. A red coloration is a positive test. Dioxane should be used as the solvent unless the compound is readily soluble in water.

c. *Ferric chloride test.* Phenols, except highly substituted ones such as trinitrophenol, give pink, purple or green colorations with ferric chloride solution. Hydroxy acids of the noncyclic type, such as lactic acid, give distinctly yellow solutions. Gallic acid gives a black precipitate. Many aromatic acids, such as benzoic and cinnamic, give tan precipitates. Of course, if the solution being tested is basic, ferric hydroxide will precipitate.

It has been established[5] that the cause of color in the phenol-ferric chloride test is due to the formation of complex coordinate ions of the

[4] Duke and Smith, *Ind. Eng. Chem., Anal. Ed.*, **4**, 201 (1940).

[5] Wesp and Brode, *J. Am. Chem. Soc.*, **56**, 1037 (1934)

type $Fe(OAr)_6^{\equiv}$, where —OAr is the ionized phenol. The color is destroyed by adding acids or bases.

$$Fe^{+++} + 6\ C_6H_5OH + 6\ HOH \rightarrow Fe(OC_6H_5)_6^{\equiv} + 6\ H_3O^+$$

Dissolve about 50 mg of the compound in 5 ml of water, or a mixture of water and alcohol. Add up to three drops of a 2.5 per cent solution of ferric chloride.

d. *Nitrochromic acid.* A mixture of nitric acid and potassium dichromate gives a blue color with certain types of organic compounds.[6] If the test is carried out as directed, a blue color will develop within 5 minutes with all the common primary and secondary alcohols, the saccharides, formaldehyde, lactic acid and tartaric acid. Some samples of commercial tertiary alcohols will give the test in about 5 minutes, but this apparently is due to small concentrations of other alcohols. The test is negative for tertiary alcohols, aldehydes (except formaldehyde), ketones, acids of the acetic series, oxalic acid, citric acid, phenols and amino compounds.

Add 5 drops of a 5 per cent solution of potassium dichromate to 5 ml of cold 7.5 N nitric acid, and add 1 ml of about 10 per cent solution of the compound to be tested. If the compound is insoluble in water, 50–100 mg of it may be added directly to the reagent and thoroughly shaken. A distinct blue color should develop within 5 minutes.

In the case of sugars, this modification of the test may be used: Add 1 ml of a 1 per cent solution of the sugar to 1 ml of concentrated nitric acid, and then add 4–5 drops of a 5 per cent solution of potassium dichromate. A blue color will develop in the cold mixture within 1 minute.

Selecting specific class tests. Chapter 6 presents a large number of tests for specific classes and subclasses. It is not intended that all of these tests shall be made on any one unknown, but it is assumed that the beginner will make all of the tests with known compounds so as to be familiar with the results of each test. If this is not feasible, it is recommended that the reader who is using the tests for an unknown also make the test with a known compound of the appropriate class for comparison.

If any clues have been obtained from previous observations, select those tests that will determine the presence or absence of the suspected functional group. If the results are negative, try tests for closely related functional groups until the compound is classified.

If no real clues have been obtained as to the classification from studies

[6] Fearon and Mitchell, *Analyst*, **57**, 372(1932).

made thus far, proceed with some systematic series of tests. For example, especially if the compound is in solubility class **W, E,** or **S,** run tests for the following classes in the order listed: esters, alcohols, anhydrides, aldehydes, and ketones, ethers and hydrocarbons. If the compound contains nitrogen, and if its classification has not been established by its solubility, alkalinity or other observations, the following are logical tests: ammonium salts, amides, amines, anilides and nitrocompounds; if all of these are negative, the tests for other classes of nitrogen compounds should be made. Records should be carefully kept of all the experiments performed, and of the results observed.

Specific Class Tests

THE chemical literature records hundreds of reagents that may be effective in the identification of organic compounds or classes of compounds. Unfortunately, however, reagents that are reliably specific for only one class of organic compounds, and will give a positive test for all members of that class, are rare. In the preparation of this work all the tests used in well-known textbooks in the field, old and new, have been considered, and most of them have been tried repeatedly in the laboratory and modified where necessary. Evaluation has been based primarily on reliability, but with proper consideration for the availability and cost of reagents and the time required for the procedure. No test has been omitted merely because it is old, nor was one included merely because it is of recent vintage. The suggested methods of testing for the various classes included in this chapter represent the most successful tests, both with knowns and unknowns, as judged by experience with beginners.

The major classes of organic compounds have been listed alphabetically under one of the first four divisions of this chapter. The divisions are based on the elements present in the major functional group or groups of the compound. For example, the first division contains those classes that do not have nitrogen, halogens, or sulfur in the major functional group; but these elements may be present in less active or subordinate groups. Acids and phenols fall in the first division; hence, if previous experience indicated that the unknown is an acid or a phenol, it should be tested for those classes. If the qualitative analysis of the compound showed that nitrogen or halogen was present, a nitro- or halo-substituted acid or phenol should be suspected. If an unknown contains nitrogen and falls in Solubility Division **C**, it should be tested for acids and phenols before the nature of the nitrogen is determined. In every case, an attempt should be made to determine the major functional group first.

The last division of this chapter includes tests that are not specific for any one chemical class, but that may yield useful information in special cases.

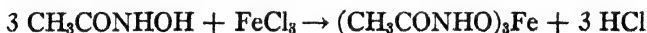
Directions for the preparation of the general solutions and special reagents used in these tests are given in the Appendix (pages 460–464).

Compounds Containing Only Carbon and Oxygen or Carbon, Oxygen, and Hydrogen in the Major Functional Group

Tests have been recently introduced[1] into qualitative organic analysis based on the direct or indirect conversion of compounds such as esters, acids, anhydrides, acid halides, alcohols, ethers, and amides into *hydroxamic acids* (RCONHOH), which in turn may be identified by means of the wine-colored *ferric hydroxamates.* Since esters may be identified directly by the hydroxamate test, they will be considered first. The chemistry involved in using the hydroxamate test to identify other classes of compounds is discussed in connection with each separate class for which this test is recommended.

6.1 Esters: The ferric hydroxamate test. Esters react with hydroxylamine to form an alcohol and a hydroxamic acid, which acid will react with ferric chloride to form ferric hydroxamate, a colored salt. Using ethyl acetate as a typical ester, the equations would be:

$$CH_3COOC_2H_5 + H_2NOH \rightarrow CH_3CONHOH + C_2H_5OH$$

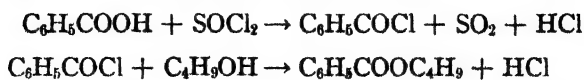
$$3\ CH_3CONHOH + FeCl_3 \rightarrow (CH_3CONHO)_3Fe + 3\ HCl$$

Anhydrides and many acyl and aroyl halides will react with hydroxylamine to give hydroxamic acids. In order to eliminate these classes when testing an unknown for an ester, add a slight excess of 10 per cent sodium hydroxide and warm the mixture to insure the conversion of anhydrides or acid halides to salts. Pipette off 2–3 drops of the insoluble material and test it for esters by the test given. ***It is important to test for esters before using the hydroxamate test for any other class of compounds.***

To 1 drop of an ester in a test tube, add 0.5 ml of a 1 *N* solution of hydroxylamine hydrochloride in methanol. Now add enough 2 *N* potassium hydroxide in methanol to make the mixture alkaline to litmus. Heat the mixture just to boiling and then cool it. Acidify the solution with dilute hydrochloric acid and add 1 drop of 10 per cent ferric chloride solution. A reddish-wine color is a positive test. If the color is too faint, add more ferric chloride.

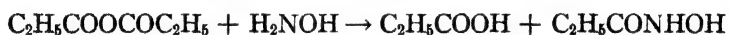
6.2 Acids. Acids may be converted to esters and thus identified indirectly by the hydroxamate test. Either phosphorous pentachloride or thionyl chloride may be used to convert the acid to the acid halide, which will react with an alcohol to form an ester; *e.g.*:

[1] Feigl, *Spot Tests*, Nordeman Pub. Co., New York, 1939; Davidson, *J. Chem. Educ.*, **17**, 81 (1940).

$$C_6H_5COOH + SOCl_2 \rightarrow C_6H_5COCl + SO_2 + HCl$$

$$C_6H_5COCl + C_4H_9OH \rightarrow C_6H_5COOC_4H_9 + HCl$$

Place 100 mg (or 2 drops) of an acid into a 6-inch test tube and add 5 drops of thionyl chloride. Immerse the tube in boiling water for 15–30 seconds. Now add 3 drops of an alcohol—*e.g.*, butyl or amyl—to the tube and again heat the mixture in boiling water for 30 seconds. Cool the tube and add 1 ml of water to hydrolyze any excess thionyl chloride. Add 1 ml of 1 *N* hydroxylamine hydrochloride solution and then enough 5 *N* potassium hydroxide in 80 per cent methanol to make the mixture alkaline to litmus. Heat just to boiling and then cool. Acidify with dilute hydrochloric acid and add a drop of 10 per cent ferric chloride solution. A reddish-wine color is a positive test.

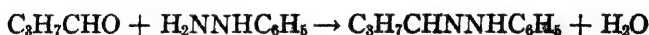
6.3 Anhydrides. Most anhydrides may be converted to hydroxamic acids without being first converted to the ester.

$$C_2H_5COOCOC_2H_5 + H_2NOH \rightarrow C_2H_5COOH + C_2H_5CONHOH$$

Add a drop of the anhydride to 0.5 ml of a 1 *N* solution of hydroxylamine hydrochloride in methanol. Heat the mixture just to boiling, cool, and add a drop of 10 per cent ferric chloride solution. The characteristic reddish-wine color of the ferric hydroxamate complex will generally develop.

If an anhydride is suspected, even though the above method produced negative results, heat 3 drops of the anhydride with 3 drops of butyl alcohol and then test for an ester by Test 6.1.

Many acyl and aroyl halides will give a positive test by the procedures here given for anhydrides, but their identity would have been suspected because of the halogen present. In such cases apply the test for halides.

6.4 Aldehydes and ketones. Many aldehydes and ketones react alike with reagents that condense with the carbonyl group. (Tests that are positive for aldehydes but not for ketones are given in Test 6.5.)

$$C_3H_7CHO + H_2NNHC_6H_5 \rightarrow C_3H_7CHNNHC_6H_5 + H_2O$$

a. Dissolve about 50 mg of phenylhydrazine hydrochloride in 10 ml of water (**Note:** 2 drops of phenylhydrazine and 1 drop of glacial acetic acid may be substituted for the phenylhydrazine hydrochloride.). Add 3 drops of the aldehyde or ketone and shake the tube vigorously. If no precipitate forms, heat the mixture to boiling, cool it, and shake again. A white or yellow precipitate is a positive test.

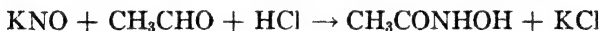
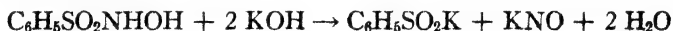
b. Instead of the phenylhydrazine used in "a," the 2, 4-dinitrophenylhydrazine may be used. Suspend 50 mg of the 2, 4-dinitrophenylhydrazine in 10 ml of ethanol and heat to boiling. Add 3 drops of the

aldehyde or ketone and boil for 1 minute. Now add 3 drops of concentrated hydrochloric acid and boil for 30 seconds. If no precipitate forms on cooling, add water dropwise. A white or yellow precipitate is a positive test.

6.5 Aldehydes. The following tests are given by aldehydes in general, but not by ketones, except where noted.

a. *Benzene sulfonhydroxamic acid test.* Dissolve a few milligrams of benzene sulfonhydroxamic acid in 0.5 ml of methanol and add a drop or crystal of the aldehyde. Now add 0.5 ml of the 2 *N* potassium hydroxide in methanol Heat the mixture just to boiling. Cool it, acidify with dilute hydrochloric acid, and add a drop of 10 per cent ferric chloride. A wine coloration is a positive test. It is reported that *o*-nitrobenzaldehyde and the *p*-hydroxy aromatic aldehydes do not respond to this test. Benzyl ketones do give the test. The exact chemistry of this reaction is in dispute, but one explanation is shown by the following equations:

$$C_6H_5SO_2NHOH + 2\ KOH \rightarrow C_6H_5SO_2K + KNO + 2\ H_2O$$

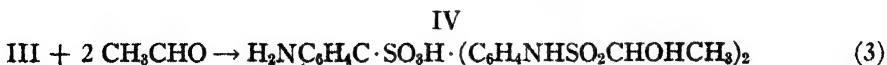
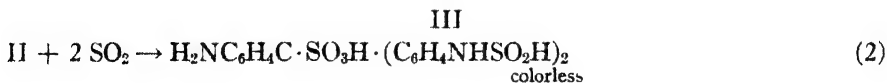
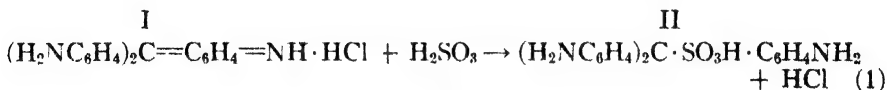
$$KNO + CH_3CHO + HCl \rightarrow CH_3CONHOH + KCl$$

In this reaction, the KNO is the salt of the hypothetical nitrosyl acid, HN=O.

b. *Schiff's test.* *p*-Rosaniline hydrochloride will react with sulfurous acid to form a leuco-sulfonic acid, which will react with more sulfurous acid to form the colorless bis-N-sulfinic acid. This acid will react with two moles of an aldehyde to give an addition complex that is unstable and loses one mole of sulfurous acid to produce a wine-purple quinonoid-type dye. The probable equations for these reactions are:

$$\underset{\text{I}}{(H_2NC_6H_4)_2C{=}C_6H_4{=}NH\cdot HCl} + H_2SO_3 \rightarrow \underset{\text{II}}{(H_2NC_6H_4)_2C\cdot SO_3H\cdot C_6H_4NH_2} + HCl \quad (1)$$

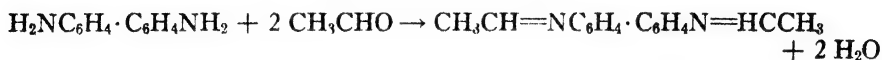
$$II + 2\ SO_2 \rightarrow \underset{\text{colorless}}{\overset{\text{III}}{H_2NC_6H_4C\cdot SO_3H\cdot (C_6H_4NHSO_2H)_2}} \quad (2)$$

$$III + 2\ CH_3CHO \rightarrow \overset{\text{IV}}{H_2NC_6H_4C\cdot SO_3H\cdot (C_6H_4NHSO_2CHOHCH_3)_2} \quad (3)$$

$$IV \rightarrow H_2SO_3 + \underset{\text{wine-purple}}{HN{=}C_6H_4{=}C(C_6H_4NHSO_2CHOHCH_3)_2} \quad (4)$$

Add 3 drops of an aldehyde to 2 ml of colorless Schiff's reagent. Do not warm the mixture. A wine-purple coloration will develop within 10 minutes. A few ketones give faint colorations with this test. There are

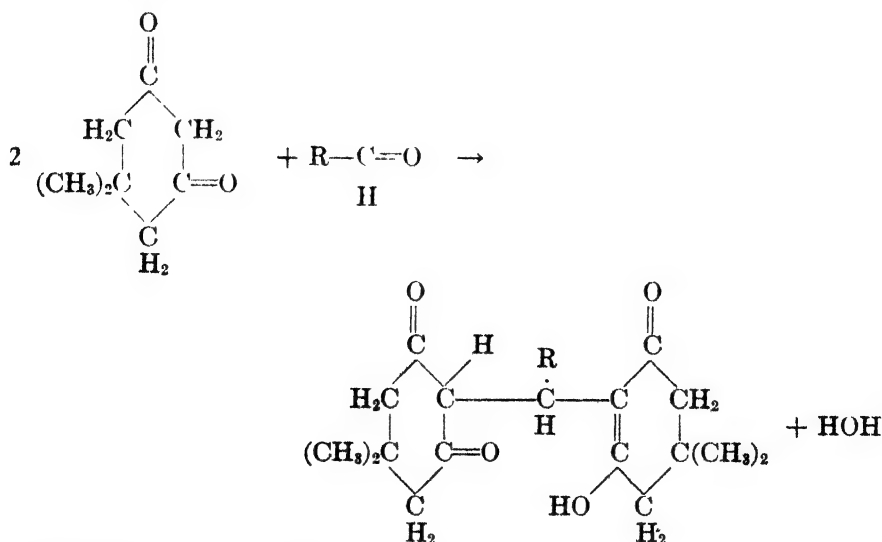
compounds other than aldehydes that will give light-pink colorations, but these colors lack the blue cast characteristic of aldehydes.

c. *Benzidine test.* A half-saturated solution of benzidine in glacial acetic acid will react with most aldehydes to give a yellow, orange, or red coloration or precipitate. The tendency is for the alkanals to form yellow colorations, which change to red on being heated, and for the aromatic aldehydes to form crystalline precipitates. The reaction seems to be a condensation reaction on both amino groups of the benzidine.

$$H_2NC_6H_4 \cdot C_6H_4NH_2 + 2\ CH_3CHO \rightarrow CH_3CH{=}NC_6H_4 \cdot C_6H_4N{=}HCCH_3 + 2\ H_2O$$

Add 3 drops of the aldehyde to 3 ml of a 3–4 per cent solution of benzidine in glacial acetic acid. The reaction will occur without the addition of heat and usually takes place immediately. *The reagent should be made up at the time it is to be used.*

d. *Methone test.* The compound 5,5-dimethylcyclohexane-1, 3-dione is often called methone, dimethone, or dimethol and is generally listed in the chemical catalogs as dimethyldihydroresorcinol. It is recommended[2] as a reagent for aldehydes and does not give the test with ketones. A milky suspension forms immediately when the reagent is added to very small amounts of aldehydes. The suspension gradually crystallizes and after several hours colorless crystals are present. For a *qualitative* test for aldehydes, the formation of the milky suspension is adequate, and it is not necessary to allow the mixture to stand.

The chemical reaction involved in this test is as follows:

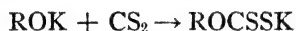
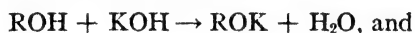
```
              O
              ‖
              C
            /   \
        H2C       CH2
  2      |         |          + R—C=O    →
    (CH3)2C       C=O             |
            \   /                 H
              C
              H2

                       O                                  O
                       ‖                                  ‖
                       C      H          R                C
                     /   \   /           .              /   \
                 H2C       C ———————— C ——— C              CH2
                  |        |          H     ‖              |          + HOH
             (CH3)2C       C=O              C              C(CH3)2
                     \   /                HO  \          /
                       C                        C
                       H2                       H2
```

² Weinberger, *Ind. Eng Chem*, *Anal Ed*, **3**, 365 (1931)

Add 50 mg of the aldehyde to 1 ml of water and then add 3 drops of a 5 per cent solution of methone in ethanol. Shake the mixture. The formation of a milky suspension within 2 minutes is a positive test for aldehydes.

c. *Oxidation test.* Aldehydes, especially the aliphatic members, are rather easily oxidized. Only a few ketones are oxidized by the relatively mild agents required for aldehydes. Aldehydes may be oxidized by such agents as the Cu^{++} and Ag^{+} ions in alkaline media. For directions, consult Test 6.37 for Benedict's, Fehling's, and Tollen's reagents.

6.6 Alcohols: a. *Xanthate test.* It has been shown[3] that the alcohols may be qualitatively detected and quantitatively estimated by reacting the potassium alkoxides with carbon disulfide to form the potassium alkyl xanthates. The test is also satisfactory for the cellosolves (monoalkyl ethers of glycol), but the carbitols (monoalkyl ethers of diethyleneglycol) yield heavy red oils instead of the customary yellow precipitates. The xanthates of tertiary alcohols are rather easily hydrolyzed but enough precipitate is formed to give a positive test.

$$ROH + KOH \rightarrow ROK + H_2O, \text{ and}$$

$$ROK + CS_2 \rightarrow ROCSSK$$

Add 1 pellet of solid potassium hydroxide to 0.5 ml of the alcohol *in a dry test tube* and heat until the KOH dissolves (very volatile alcohols require a reflux condenser). Cool the tube and add 1 ml of ether. Add, dropwise, carbon disulfide until a pale-yellow precipitate forms. If a precipitate does not form by the time 0.5 ml of carbon disulfide has been added, the compound is not an alcohol.

A confirmatory test for the xanthate may be made by reacting it with a very dilute solution of a molybdenum salt.[4] Separate the precipitated xanthate and add about 5 mg of it to 2 drops of a solution containing about 1 mg of ammonium molybdate. On the addition of 4 drops of 2 *N* hydrochloric acid, a red-blue coloration develops. The color is due to the complex $(ROCSSH)_2MoO_3$.

b. *Hydroxamate test.* Alcohols may be converted to esters by reaction with acetyl chloride. Tertiary alcohols are partly converted to alkyl chlorides when they are treated with acetyl chloride, owing to the reaction of the liberated hydrogen chloride on another molecule of the alcohol. This can be avoided by introducing dimethylaniline into the mixture to react preferentially with the hydrogen chloride. The di-

[3] Whitmore and Lieber, *Ind. Eng. Chem., Anal. Ed.*, 7, 127 (1935).

[4] Mellan, *Organic Reagents in Inorganic Analysis*, The Blakiston Co., Philadelphia, 1941, p. 472.

methylaniline may be omitted if the alcohol is known not to be a tertiary alcohol.

Mix 0.1 ml of acetyl chloride with 0.1 ml of dimethylaniline and add 0.2 ml of the alcohol. Shake the mixture frequently for 5 minutes. Add about 1 gram of ice, or add, dropwise and with shaking, 1 ml of cold water to decompose the remaining acetyl chloride. Pour the mixture into a small test tube so that the stratified layers may be easily distinguished. Remove 2–3 drops of the upper layer and test for esters by Test 6.1.

c. *Test to distinguish primary, secondary, and tertiary alcohols.* A distinction may be made among the three subclasses of alcohols by the rates of their conversion to alkyl chlorides when reacted with a solution of zinc chloride in concentrated hydrochloric acid (Lucas[5] reagent). The alcohols containing up to 6 carbon atoms are soluble in this reagent. This test is not applicable to other alcohols.

Mix 0.5 ml of the alcohol with 3 ml of the reagent. Stopper the tube and shake it vigorously. Allow the tube to stand at 25–30°. A reaction is detected by a clouding of the solution, due to the formation of an insoluble alkyl halide. Tertiary alcohols react immediately; secondary alcohols react within 2–3 minutes; primary alcohols require a much longer time.

If there is any doubt as to whether the alcohol is secondary or tertiary, mix 0.5 ml of the alcohol with 3 ml of concentrated hydrochloric acid. Secondary alcohols do not convert to halides under these conditions, whereas tertiary alcohols will convert within 10 minutes.

The cloudiness of the solution, which is caused by an emulsion of the alkyl halide in the solvent, will clear up on standing, and a separate layer of the alkyl chloride will form. If the separate layer does not form, it is likely that the alcohol detected was only an impurity in a less reactive alcohol.

6.7 Tests for carbohydrates: a. *Water-soluble compounds:* (1) *Monosaccharides.* The monosaccharides are more easily oxidized than the disaccharides and hence may be oxidized by the cupric ion in acid solution. Barfoed's reagent is a solution of copper acetate in acetic acid. All of the common sugars, except sucrose, may be oxidized by cupric ion in alkaline solution (Benedict's reagent or Fehling's reagent, Test 6.37).

Mix 1 ml of Barfoed's reagent with 1 ml of about a 5 per cent solution of the sugar in water. Place the mixture in a bath of boiling water. If the sugar is a monosaccharide, the reddish precipitate of cuprous oxide

[5] Lucas, *J. Am. Chem. Soc.*, 52, 802, (1930).

will form within 2 minutes. Do not consider a precipitate that forms after that time, since disaccharides will reduce the reagent slowly.

(2) *Ketoses.* The Seliwanoff test for ketoses is based on the conversion of the ketose to hydroxymethylfurfural and its subsequent condensation with resorcinol to form colored complexes.

Mix 1 ml of Seliwanoff's reagent with 1 ml of about a 5 per cent solution of the sugar in water. Heat the mixture to boiling. A red color develops within 2 minutes if the sugar is a ketose. Long standing, or prolonged heating, will develop the color with aldoses.

(3) *Pentoses.* The Tollen's test for pentoses is based on the reaction of the pentose with hydrochloric acid to form furfural, which is then condensed with phloroglucinol to yield red-colored complexes. Other sugars may produce yellow, orange, or brown colors.

Dissolve about 10 mg of the sugar in 5 ml of 6 *N* hydrochloric acid and add about 10 mg of phloroglucinol. Boil the mixture for 1 minute. A red coloration indicates a pentose.

(4) *Osazone formation.* The methods for forming osazones and a discussion of them are given in Chapter 12, pages 303–304.

b. *Water—insoluble carbohydrates:* (1) *Iodine test.* Suspend a few milligrams of the substance in water and add 2 drops of a saturated aqueous solution of iodine. Starch gives a blue color, glycogen and the higher dextrins give red colors; inulin and the lower dextrins do not give colors. None of these substances reduce Benedict's reagent until they are hydrolyzed.

(2) *Hydrolysis.* Suspend 100 mg of the substance in 15 ml of water and shake the tube. Glycogen forms an opalescent solution without heating, whereas starch forms an opalescent solution after heating. Add 0.5 ml of dilute hydrochloric acid to the tube and boil the mixture for 10 minutes. Cool the solution and neutralize it. Test for sugars.

6.8 Esters: a. *Hydroxamate test.* Follow the directions given in Test 6.1, including the method for eliminating anhydrides and acid halides.

b. *Hydrolysis.* A rapid method for hydrolyzing esters has been proposed[6] that allows the recovery of the relatively pure alcohol, and also allows the formation of a derivative of the acid without its separation from the solvent. If the alcohol produced by hydrolysis is glycerol or a glycol, it may not be recovered but the acid may still be identified. The method is given as Procedure 10.13, page 232.

[6] Redemann and Lucas, *Ind. Eng. Chem., Anal. Ed*, **9**, 521 (1937)

6.9 Tests for ethers: a. *Esterification.*[7] A great many of the ethers may be hydrolyzed and converted into acetate esters by heating a mixture of the ether, acetic acid, and concentrated sulfuric acid. The reaction is not complete but sufficient ester is formed to give the hydroxamate test for esters (Test 6.1). The presence of unchanged ether does not interfere with this test.

Mix 0.5 ml of the ether with 2 ml of glacial acetic acid and 0.5 ml of concentrated sulfuric acid. Reflux the mixture for 5 minutes and distil 1 drop. Test this drop for esters by Test 6.1 (be sure that enough potassium hydroxide solution is used to make the mixture alkaline). If the drop of distillate does not give a positive test for esters, cool the mixture that was refluxed and add 5 ml of ice water to it. If a separate liquid phase separates, test it for esters. It is sometimes advisable to extract the mixture with 0.5 ml of benzene and test the benzene extract for esters.

b. *The iodine test for ethers.* Add 0.5 ml of an ether or hydrocarbon to 1 ml of a light-purple solution of iodine in carbon disulfide. Ethers change the color of the solution to tan. Aromatic hydrocarbons do not affect the purple color, whereas noncyclic hydrocarbons produce a light-tan color without destroying the violet color of the iodine solution.

6.10 Tests for hydrocarbons. Hydrocarbons are identified more by elimination than by direct proof. If the compound fails to give a positive test for some active functional group, and if it fails to destroy the purple color of iodine in carbon disulfide (Test 6.9), it should be suspected of being a hydrocarbon. Consider the data obtained in Chapter 3 about unsaturation, aromatic character, and general physical properties.

6.11 Phenols. If a phenol is indicated by its solubility data and by Test 5.6, its presence may be confirmed by one or more of the following tests.

a. *Indicator formation.* Most phenols condense with phthalic anhydride to form indicators that have blue, purple, red, or green colors in alkaline solution. Phenol itself condenses with phthalic anhydride to form phenolphthalein. *Para*-substituted phenols are not detectable by this test.

Add 100 mg of the phenol, 300 mg of phthalic anhydride, and 200 mg of anhydrous zinc chloride to a test tube. Heat the mixture for 1 minute to fuse the mass and then cool it. Slowly add 1–2 per cent sodium hydroxide solution and shake the tube. When the solution is alkaline, note the color. It is important not to add too much excess sodium hy-

[7] The esterification test for ethers was proposed in a private communication by David Davidson, Brooklyn College, N. Y.

droxide as many indicators lose their characteristic color in excess alkali.

b. *Nitrous acid test.* This is a modification of Liebermann's test for nitroso compound (Test 6.22) and is given by phenols that have the *ortho* or *para* position unsubstituted. Apparently the color is produced by the formation of the isomeric quinonoid structures of the nitroso phenols. It may be assumed that the color is due to a reaction between the phenol and the nitroso phenol.

$$C_6H_5OH + HONO \rightarrow ONC_6H_4OH \rightleftarrows HON{=}C_6H_4{=}O$$

Add about 50 mg of the phenol to 1 ml of concentrated sulfuric acid and then add 1 crystal of sodium nitrite. Shake the tube and warm it slightly. A positive test is indicated if a blue or purple color develops. Cautiously pour the mixture into 5 ml of water. The color should change to purplish red.

c. *Millon's test.* This test is for monohydroxy phenols that have at least one *ortho* position open. It is also given by tyrosine, tyrosine-containing proteins, phenolic acids, and other compounds that have one phenolic group with an *ortho* position open. Add 50 mg of the phenol to 1 ml of Millon's reagent. Place the tube in a beaker of water and heat it to boiling. A red color will develop. The chemistry involved in this color formation is not clear.

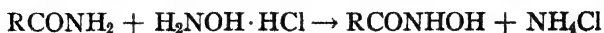
Compounds Containing Nitrogen in the Major Functional Group

The classes included in this division may contain halogens or sulfur in subordinate groups, for example, the halo anilines. If both sulfur and nitrogen are present in the major functional group—*e.g.*, sulfonamides—the listing will be found on page 142.

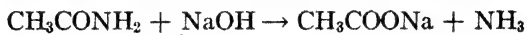
6.12 Ammonium salts. Hypochlorite solutions, ammonium ions, and phenol react to give a blue color. It appears that the hypochlorite oxidizes the ammonia to nitrous acid, which then reacts with the phenol as in Test 6.11-b.

Mix 1 ml of a 4 per cent aqueous solution of a phenol with 1 ml of 5 per cent aqueous sodium hypochlorite in a test tube. Add a crystal of an ammonium salt or a few drops of a solution of such a salt. Warm the mixture. A blue color develops in the presence of very small quantities of the ammonium ion.

6.13 Aliphatic amides: a. *Hydroxamate test.* Aliphatic amides may be readily converted to hydroxamic acids by hydroxylamine hydrochloride and then identified by the usual ferric hydroxamate test. Salicylamide is the only aromatic amide known to give this test.

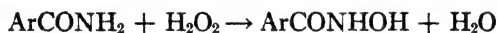
$$RCONH_2 + H_2NOH \cdot HCl \rightarrow RCONHOH + NH_4Cl$$

Add 100 mg of the amide to 1 ml of the hydroxylamine hydrochloride reagent and boil the mixture gently for 3 minutes. Cool the tube and add a drop of 10 per cent ferric chloride solution. A wine or purple color is a positive test.

b. *Hydrolysis.* Amides may be hydrolyzed by a sodium hydroxide solution. Under the conditions given below, the amides of aliphatic acids will be hydrolyzed but aromatic amides and sulfonamides will not.

$$CH_3CONH_2 + NaOH \rightarrow CH_3COONa + NH_3$$

This test must be used with discretion because several classes of compounds will yield ammonia or volatile amines, which may be confused with ammonia. Most of these interfering classes will fall in different Solubility Divisions from the amides. Classes known to interfere are the salts of aliphatic amines, hydrazines, and a few aromatic amines.

Boil 200 mg of the amide with 5 ml of 10 per cent aqueous sodium hydroxide solution for 3 minutes. Test for the evolution of ammonia, either by odor, moist red litmus, or by absorbing the evolved gas in water and using Test 6.12.

6.14 Aromatic amides: a. *Hydroxamate test.* Aromatic amides, but not sulfonamides, are converted directly to hydroxamic acids by hydrogen peroxide in the presence of ferric chloride. Hence, the ferric hydroxamate test is given directly.

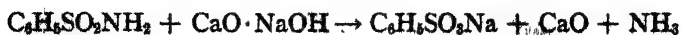
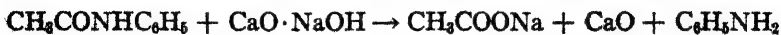
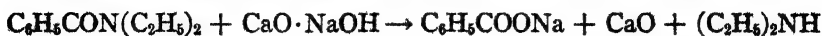
$$ArCONH_2 + H_2O_2 \rightarrow ArCONHOH + H_2O$$

Suspend 50 mg of the aromatic amide in 5 ml of water. Add 1 drop of 10 per cent ferric chloride and 0.5 ml of 3 per cent hydrogen peroxide. Slowly heat the mixture to boiling. The characteristic wine color of ferric hydroxamate will develop. Prolonged heating seems to destroy the color. Organic solvents should be absent.

b. *Soda-lime test.* Dry fusion with soda-lime will decompose most of the simple amides; that is, aliphatic amides, aromatic amides, and sulfonamides, and also the N-substituted amides, such as the anilides and N-dimethylbenzamide. The fusion of the simple amides yields ammonia, whereas the N-substituted amides yield primary or secondary amines.

$$C_2H_5CONH_2 + CaO \cdot NaOH \rightarrow C_2H_5COONa + CaO + NH_3$$

$$C_6H_5CON(C_2H_5)_2 + CaO \cdot NaOH \rightarrow C_6H_5COONa + CaO + (C_2H_5)_2NH$$

$$CH_3CONHC_6H_5 + CaO \cdot NaOH \rightarrow CH_3COONa + CaO + C_6H_5NH_2$$

$$C_6H_5SO_2NH_2 + CaO \cdot NaOH \rightarrow C_6H_5SO_3Na + CaO + NH_3$$

The various kinds of amides that give this test may be distinguished by the character of the distillate and by the other tests for amides. If the amide gives neither Test 6.13-b for aliphatic amides nor Test 6.31 for sulfonamides, it should be considered an aromatic amide. If both ammonia and an amine are found in the distillate, it should be assumed that the ammonia was formed by decomposition of an N-substituted amide. Complete fusion of the salts of the acids with excess sodium hydroxide will cause a reaction between the salts and the sodium hydroxide to form a hydrocarbon and sodium carbonate or sodium sulfite. The hydrocarbon will generally distil. A distillate should be examined to prove it is an amine and not a hydrocarbon before this test is considered "positive" for amides.

Thoroughly mix 0.5 g of the amide with 2 g of dry soda-lime and place the mixture in a dry Pyrex test tube. Attach a delivery tube that extends to the bottom of a well-cooled test tube, which acts as a receiver and contains a few drops of water. Heat the tube containing the soda-lime by moving a flame up and down the tube. After the mixture begins to fuse, continue the application of a hot flame for 1 minute. Test the gas that distils and test the distillate for any base besides ammonia.

6.15 Anilides. Anilides will decompose when fused with soda-lime (Test 6.14b), and the aniline that distils may be identified by Test 6.16-c. Anilides usually hydrolyze sufficiently to give a positive test for aniline by the carbylamine reaction (Test 6.16-e). Most anilides produce a rose or purple color by Tafel's test, which is given below. The chemistry of this color formation is not known.

Without heating, shake 100 mg of the compound with 3 ml of concentrated sulfuric acid. Add 50 mg of finely powdered potassium dichromate.

6.16 Tests for amines. Simple amines, particularly the primary amines, are easily identified, both by solubility and by specific tests. Many of the substituted aromatic amines, even if they are primary amines, fail to dissolve in dilute acids. This is even more true of the polyaryl amines. Since no specific test works perfectly on all amines, it is wise to test any nitrogen-containing compound that is not easily classified by at least two of the tests for amines.

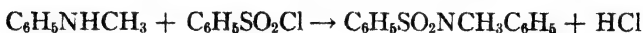
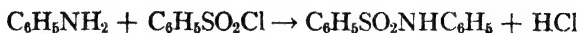
a. *Acid salts of amines.* Neutralize a solution of the salt with 10 per cent sodium hydroxide. Remove the free amine by distillation or extraction with ether and test it.

b. *Reaction with benzenesulfonchloride.* This compound, known as the Hinsberg reagent, is useful in most cases for distinguishing primary, secondary, and tertiary amines. It reacts with both primary and

secondary amines but not with tertiary amines. The substituted sulfonamides that form as a result of the reaction with primary amines are soluble in dilute sodium hydroxide; whereas those from secondary amines are not soluble, unless the compound is amphoteric, such as an alklylamino-substituted acid or phenol. Some of the substituted amines do not give this test.

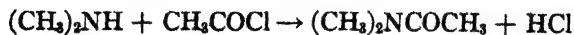
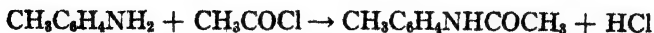
$$C_6H_5NH_2 + C_6H_5SO_2Cl \rightarrow C_6H_5SO_2NHC_6H_5 + HCl$$

$$C_6H_5SO_2NHC_6H_5 + NaOH \rightarrow C_6H_5SO_2NNaC_6H_5 + HOH$$

$$C_6H_5NHCH_3 + C_6H_5SO_2Cl \rightarrow C_6H_5SO_2NCH_3C_6H_5 + HCl$$

Place 200 mg of the amine, 0.3 ml of benzenesulfonchloride, and 10 ml of 5 per cent sodium hydroxide in a large test tube or small flask. Firmly insert a stopper and shake the container vigorously for 2 minutes. If the vessel heats up, hold it under running water to cool it. Test the mixture with litmus and, if it is acidic, make it alkaline and shake it again. If all the original compound dissolves, it was a primary amine. If there is a residue, either solid or liquid, remove it and test its solubility in 25 per cent hydrochloric acid. If the residue is soluble in the acid, it indicates that it was a tertiary amine that had not reacted with the reagent. If the residue fails to dissolve in the acid, it probably was a secondary amine. It is well, however, to examine the remaining material to see if it is the same as the original compound. This may be done by purifying it and taking the melting point. The fact that it failed to dissolve in the hydrochloric acid or to react with the reagent does not rule out the possibility of its being an amine, but most amines may be classified by this test. Additional information may be obtained by consulting Procedures 11.18–11.20, pages 259–260.

c. *Reaction with acetyl chloride.* This active reagent will react with water, alcohols, and all other compounds that have an easily replaced hydrogen, including many primary and secondary amines. However, many of the substituted anilines fail to react with acetyl chloride. This is particularly true of those that have nitro groups *ortho* or *para* to the amino group. These same amines fail to dissolve in dilute hydrochloric acid. When the amines react with acetyl chloride, they form N-substituted amides.

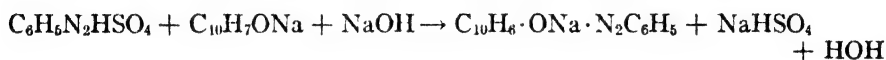
$$CH_3C_6H_4NH_2 + CH_3COCl \rightarrow CH_3C_6H_4NHCOCH_3 + HCl$$

$$(CH_3)_2NH + CH_3COCl \rightarrow (CH_3)_2NCOCH_3 + HCl$$

Place 100 mg of the amine in a dry test tube and add 2 drops of acetyl chloride. If no reaction seems to occur, warm the tube slightly. The

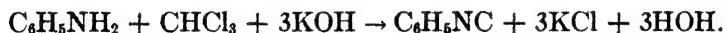
N-substituted amide will form. It may be purified and used as a derivative of the amine.

d. *Diazotization test for primary arylamines.* This seems to be the best test for substituted amines that do not dissolve in dilute hydrochloric acid or react with acetyl chloride. It is recommended that this test be made on all nitrogen compounds that have not been classified up to this point. The primary arylamines are converted to the diazonium salts by nitrous acid. At low temperatures, these salts are stable and will couple in the *alpha* position with the sodium salt of β-naphthol.

$$C_6H_5NH_2 + HONO + H_2SO_4 \rightarrow C_6H_5N_2HSO_4 + 2\ HOH$$

$$C_6H_5N_2HSO_4 + C_{10}H_7ONa + NaOH \rightarrow C_{10}H_6 \cdot ONa \cdot N_2C_6H_5 + NaHSO_4 + HOH$$

Prepare about 100 ml of a mixture of crushed ice, salt, and water to be used as a chilling bath. In one tube, mix 1 ml of water, 5 drops of concentrated sulfuric acid, and 100 mg of the primary arylamine. A second tube should contain 1 ml of a 10 per cent solution of sodium nitrite. Dissolve 200 mg of β-naphthol in 2 ml of 10 per cent sodium hydroxide in a third tube. Chill all three solutions in the ice bath. Dropwise and with shaking, add the sodium nitrite solution to the acidified amine. Now add, dropwise, the sodium naphthoxide. A red color indicates a primary arylamine. Other monohydroxy phenols may be used, but the color is not always red.

e. *Carbylamine test for primary amines.* Most primary amines will react with chloroform and potassium hydroxide to form the nauseatingly odored isocyanides. The test is very delicate and will be given by small concentrations of primary amines if they are present in other amines as impurities. *This test is more useful with aromatic amines than others.*

$$C_6H_5NH_2 + CHCl_3 + 3KOH \rightarrow C_6H_5NC + 3KCl + 3HOH.$$

Mix 50 mg of the primary arylamine with 2 drops of chloroform and 1 ml of 2 *N* potassium hydroxide in methanol. Warm the mixture slightly and note the odor.

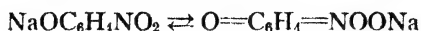
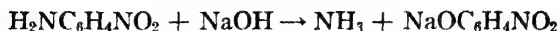
f. *Arylamines with nitro or nitroso groups in the* ortho *or* para *positions.* If a nitro or nitroso group is in the *ortho* or *para* position with respect to an amino group, the amino group may be replaced by a hydroxyl group by boiling the compound with 10 per cent sodium hydroxide solution. Thus the substituted amines are converted to substituted phenols. The test is positive with primary arylamines and also with the N-alkyl-substituted amines. Ammonia or an alkylamine is liberated. The cause of the color change from lemon-yellow to orange or red is ap-

parently due to the formation of a quinonoid structure by the sodium salt.

$$(CH_3)_2NC_6H_4NO + NaOH \rightarrow (CH_3)_2NH + NaOC_6H_4NO$$

$$NaOC_6H_4NO \rightleftarrows O{=}C_6H_4{=}NONa$$

$$H_2NC_6H_4NO_2 + NaOH \rightarrow NH_3 + NaOC_6H_4NO_2$$

$$NaOC_6H_4NO_2 \rightleftarrows O{=}C_6H_4{=}NOONa$$

Heat a mixture of 100 mg of the amine with 5 ml of 10 per cent sodium hydroxide until the mixture boils. Test the vapors for ammonia and amines and note the change in color of the solution from yellow to orange-red or red.

g. *Primary and secondary alkylamines.* The Rimini test for primary alkylamines and the Simon test for secondary alkylamines are both sensitive tests. Mixtures of the two types of amines will give positive reactions with both tests, except that the test for secondary amines is obscured by a large excess of primary amines. The chemistry of the color formation in these tests is not known. The amines should be water-soluble to give satisfactory results.

(1) *Primary amines.* Add 1 ml of acetone to 5 ml of a dilute aqueous solution of the amine and then add 1 drop of a 1 per cent aqueous solution of sodium nitroprusside. A definite violet-red coloration will develop within 1 minute. The acetone used in this test must be free of acetaldehyde.

(2) *Secondary amines.* Add 1 ml of a 5 per cent solution of acetaldehyde to 5 ml of a dilute aqueous solution of the amine and then add 1 drop of a 1 per cent solution of sodium nitroprusside. A blue color will develop within 5 minutes. The color changes, on standing, to green and finally to yellow.

h. *Chloranil test.* Chloranil (tetrachloroquinone) produces red, blue, or green colorations with most amines. Some phenols and the compounds containing divalent sulfur react with chloranil to give amber or orange colors. The structures responsible for the colors have not been determined. Add 3 drops of a saturated solution of chloranil in dioxane to 1 drop of the compound under examination.

6.17 Hydrazines. The hydrazines liberate ammonia when heated with 10 per cent sodium hydroxide and reduce Tollen's or Benedict's reagents (Test 6.37). A more specific test is based on their ability to form hydrazones with aldehydes or ketones, as in Test 6.4.

Suspend 0.1 ml of the hydrazine in 1 ml of water. Add a few drops of acetic acid to dissolve the hydrazine and then add a few drops of a 5 per cent solution of acetaldehyde. A precipitate will form.

6.18 General test for nitro, nitroso, azoxy, and azo compounds. The following test will identify a compound as belonging to one of the four classes listed. More specific tests for nitro and nitroso compounds are given in later tests. The test is based on the production of hydroxylamines, hydrazines, or hydrazo compounds, all of which are reducing agents, and then testing the reducing action by Tollen's reagent. It is therefore necessary to test the reducing power of the compound under examination before this test is made. To do this, dissolve or suspend 100 mg of the compound in 2 ml of ethanol and add 1 ml of Tollen's reagent. Allow to stand for 5 minutes. A silver coating or black precipitate indicates a positive test, in which case there is no need to proceed with this test.

a. Dissolve or suspend 200 mg of the compound in 3 ml of hot 50 per cent ethanol. Add 3 drops of concentrated acetic acid and about 100 mg of zinc dust. Heat the mixture just to boiling and set it aside for 5 minutes. Filter the mixture through a moistened paper. Divide the filtrate into two parts. Add one part of the filtrate to 2 ml of Tollen's solution (Test 6.37) and allow the mixture to stand for 5 minutes. If a black precipitate or a silver mirror forms, the compound is a nitro, nitroso, azoxy, or azo compound. If this test is positive, use the second part of the filtrate for part "b."

b. Add 1 drop of benzoyl chloride to the filtrate and warm the mixture. Add a drop of concentrated hydrochloric acid and a drop of 10 per cent ferric chloride solution. A wine coloration (ferric hydroxamate) indicates that the original compound was a nitro or nitroso compound.

6.19 Nitro compounds. It has been shown[8] that compounds containing one or more nitro groups will oxidize ferrous hydroxide to ferric hydroxide. The color change is from green to brown. In addition to nitro compounds, the only classes known to oxidize ferrous hydroxide are nitroso compounds, quinones, hydroxylamines, nitrites, and nitrates. They are not so common as the nitro compounds and may be identified by other tests.

$$C_6H_5NO_2 + 4\ HOH + 6\ Fe(OH)_2 \rightarrow C_6H_5NH_2 + 6\ Fe(OH)_3$$

In a 3-inch test tube, mix about 20 mg of the nitro compound with 1.5 ml of a freshly prepared 5 per cent solution of ferrous ammonium sulfate. Add 1 drop of 3 *M* sulfuric acid and 1 ml of 2 *N* potassium hydroxide in methanol. Stopper the tube quickly and shake it. A positive test is indicated by the precipitate turning brown within 1 minute. The use of the small tube is required so that very little air will come in contact

[8] Hearon and Gustavson, *Ind. Eng. Chem., Anal. Ed.*, 9, 352 (1937).

with the ferrous hydroxide. If a larger tube is used, the air must be displaced immediately by blowing natural gas or some other inert gas through the tube.

6.20 Dinitro and trinitro compounds. If the presence of a nitro group is indicated by Test 6.19, the following test[9] is very useful in estimating the number of nitro groups present in benzene derivatives. The reagent is a mixture of acetone and a sodium hydroxide solution. Mononitro compounds do not produce color changes, whereas most derivatives of benzene containing two nitro groups give an immediate purplish blue color, and the trinitro compounds give a deep red color. The chemistry involved in this test has not been proved. The test is extremely sensitive. The presence of amino, alkylamino, acylamino, hydroxy, or acylated hydroxy groups on the benzene nucleus interfere with the test. The following compounds are important exceptions to the general color rules; their colors, are given below:

3, 5-dinitrosalicylic acid	yellow
2, 4-dinitrophenol	yellow-orange
2, 4-dinitroresorcinol	brownish-green
2, 4-dinitroacetanilide	reddish-orange
1, 4-dinitrobenzene	greenish-yellow
1, 2-dinitrobenzene	none
2, 4-dinitroaniline	red

Add 100 mg of the compound to 10 ml of acetone, and then add 3 ml of 5 per cent sodium hydroxide solution while shaking the tube. The colors develop quickly: purplish blue for dinitro compounds, and deep red for trinitro compounds (except as noted above).

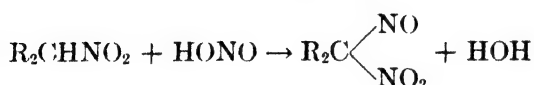
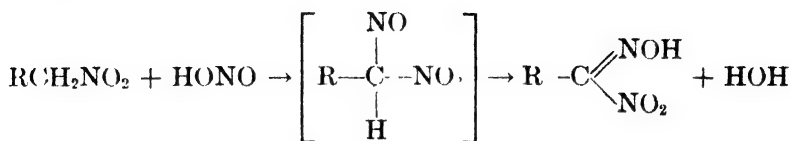
6.21 The nitroparaffins. The nitroparaffins may be reduced to hydroxylamine derivatives. Therefore, they give positive tests in both the "a" and "b" parts of Test 6.18. The test for the nitrocompounds (Test 6.19) is given by some but not all of the nitroparaffins. For example, nitromethane and 2-nitropropane give positive results, but nitroethane and 1-nitropropane fail to oxidize the ferrous hydroxide under the conditions of this test. By vigorous reduction the nitroparaffins may be converted to primary amines.

The action of nitrous acid on the nitroparaffins in alkaline solution may be used to distinguish primary, secondary, and tertiary nitroparaffins. Under the conditions given in the test below, primary nitroparaffins produce a reddish-amber color, secondary nitroparaffins a sky-blue color, and tertiary nitroparaffins do not produce any color.

[9] Bost and Nicholson, *Ind. Eng. Chem., Anal Ed.*, 7, 190 (1935).

Nitrous acid reacts with a primary nitroparaffin to yield a nitrolic acid. The salts of the nitrolic acids are red in solution (these salts are explosive when dry). Nitrous acid reacts with a secondary nitroparaffin to yield a pseudonitrole. These compounds are blue in solution. Nitrous acid fails to react with tertiary nitroparaffins. The equations for typical reactions are given below:

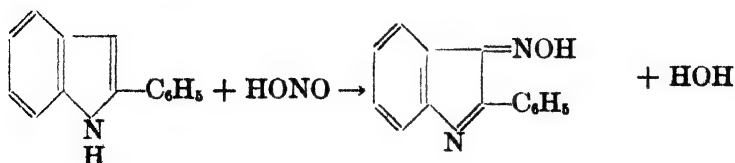
$$RCH_2NO_2 + HONO \rightarrow \left[R-\overset{\displaystyle NO}{\underset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-NO_2 \right] \rightarrow R-C\begin{matrix} \nearrow NOH \\ \searrow NO_2 \end{matrix} + HOH$$

$$R_2CHNO_2 + HONO \rightarrow R_2C\begin{matrix} \nearrow NO \\ \searrow NO_2 \end{matrix} + HOH$$

Add 5 drops of the nitroparaffin to 2 ml of 10 per cent sodium hydroxide. Allow the mixture to stand for 3 minutes. Add 1 ml of 10 per cent sodium nitrite solution and then add dropwise 10 per cent sulfuric acid, but do not add enough acid to neutralize fully the mixture.

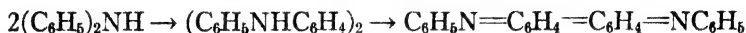
6.22 Nitrosoamine compounds. This is the same as Test 6.11-b, except that an organic nitroso compound is used instead of sodium nitrite. The test is given by compounds where the nitroso group is attached to nitrogen but is generally not given when the nitroso group is attached to carbon. The nitroso compound reacts with the sulfuric acid to generate nitrous acid, which converts the phenol into a nitrosophenol. The blue color is probably due to the monomeric nitrosophenol (the dimer of nitrosophenol is colorless) and the red color to the ionized isomer, quinone monoxime.

Dissolve two drops of phenol in 1 ml of concentrated sulfuric acid. Add 50 mg of the nitroso compound. Shake the tube and warm it slightly. A blue color will develop. Carefully pour the acid mixture into 5 ml of cold water. The blue color will change to red.

6.23 Alkyl nitrites. Care should be taken in handling the alkyl nitrites as they have a pronounced action on the heart. They may be detected by the fact that they will react with 2-phenylindole to precipitate 3-isonitroso-2-phenylindole.

$$\text{(2-phenylindole, N–H)}-C_6H_5 + HONO \rightarrow \text{(3-isonitroso-2-phenylindole: }=NOH,\ -C_6H_5,\ N\text{)} + HOH$$

Dissolve 100 mg of 2-phenylindole in boiling ethanol and add 100 mg of the nitrite. On cooling, the 3-isonitroso-2-phenylindole will precipitate. It may be recrystallized from amyl acetate as yellow needles and has a melting point of 280°.

6.24 Nitrates. Both nitrites and nitrates act as oxidizing agents on diphenylamine in sulfuric acid. Since the test is very sensitive, enough nitrate radicals are liberated from organic nitrates by sulfuric acid to give the test. Diphenylamine is first oxidized to diphenylbenzidine, which is further oxidized to the quinonoid form.

$$2(C_6H_5)_2NH \rightarrow (C_6H_5NHC_6H_4)_2 \rightarrow C_6H_5N{=}C_6H_4{=}C_6H_4{=}NC_6H_5$$

Add 100 mg of the compound to be tested to 3 ml of a reagent made by dissolving 200 mg of diphenylamine in 100 ml of concentrated sulfuric acid. A blue color is a positive test.

6.25 Oximes, hydrazones, and semicarbazones. All three of these classes may be hydrolyzed by concentrated hydrochloric acid and thus converted into the hydrochloride salts of hydroxylamine, the hydrazine, and semicarbazide, respectively.

$$C_6H_5CH{=}NOH + HOH + HCl \rightarrow C_6H_5CHO + HONH_2 \cdot HCl$$

$$(CH_3)_2C{=}NNHC_6H_5 + HOH + HCl \rightarrow (CH_3)_2CO + C_6H_5NHNH_2 \cdot HCl$$

$$CH_3CH{=}NNHCONH_2 + HOH + HCl \rightarrow CH_3CHO + H_2NCONHNH_2 \cdot HCl$$

The salt resulting from the acid hydrolysis of the unknown may be readily tested for hydroxylamine hydrochloride by the hydroxamate test. If it is found present, it was formed from an oxime. If the test for hydroxylamine is negative, the hydrochloride salt may be condensed with benzaldehyde or some other aldehyde or ketone, by the methods used for preparing derivatives. The melting point of the derivative will identify the hydrochloride salt.

Place 200 mg of the compound in a test tube containing 2 ml of concentrated hydrochloric acid. Immerse the tube in boiling water for 5 minutes and then evaporate the mixture to dryness on a water bath. Treat the residue with 5 ml of water. Filter if the solution is not clear. To test the solution for hydroxylamine hydrochloride, which will be formed if the original compound was an oxime, take 1 ml of the solution and add 1 drop of benzoyl chloride. Make the mixture alkaline with alcoholic potassium hydroxide and heat just to boiling. Cool and acidify the solution with hydrochloric acid. On the addition of 1-2 drops of ferric chloride, a wine color should develop if the original compound was an oxime. If the test is negative, test the remaining solu-

tion of the hydrochloride, formed by evaporation, for hydrazines and semicarbazide (pages 246 and 256).

Compounds Containing Halogen in the Major Functional Group

It should be noted that many of the compounds containing halogen have some other group in the molecule that is more reactive than the halogen-containing group. Such classes as the halogen-substituted acids, phenols, amines, and sulfonic acids will naturally be identified by the functional-group tests for acids, phenols, or amines, and not as halogen compound. The presence of halogen will, of course, help to identify the individual compound when the proper class is determined. The salts of halogen acids with amines may be detected by their solubility classification. Their identity may be established by Test 6.16-a.

6.26 Acyl, aroyl, and sulfonyl halides. This test is the reverse of Tests 6.16-b, c, where the acid halides were used to detect amines. By using aniline as the amine, the acid halides may be detected by the formation of anilides. Most anilides may be recrystallized from hot water and used as derivatives for the identification of the specific acid halide.

Add 2 drops of the acid halide to 3 drops of aniline. Now add 1 ml of cold water. The anilides are colorless solids, which are only slightly soluble in cold water.

6.27 Distinguishing alkyl and aryl halides. The halogen acid salts of amines and the acid halides will form precipitates of the silver halides when treated with cold aqueous silver nitrate. The alkyl halides and aryl halides do not react appreciably with cold aqueous silver nitrate. The following tests give positive results with alkyl halides but negative with aryl halides, except as noted in each test.

a. *Alcoholic silver nitrate.* Alkyl bromides and iodides precipitate the silver halides when treated with alcoholic silver nitrate. It should be recalled that compounds like benzyl bromide act like alkyl halides.

Add 2 drops of the halogen compound to 0.5 ml of a saturated solution of silver nitrate in ethanol. Aryl halides do not react.

b. *Hydrolysis.* The alkyl halides hydrolyze much more readily than the aryl halides. In the following test, all the alkyl halides will cause the precipitation of silver halide but the aryl halides give only slight precipitates.

Mix 100 mg of the halogen compound with 5 ml of 5 per cent alcoholic solution of potassium hydroxide and reflux the mixture for 5 minutes.

Cool the mixture and add 10 ml of distilled water. Acidify the solution with dilute nitric acid. Unless the solution is clear, filter it. Add 2 drops of 5 per cent silver nitrate solution.

c. *Mercaptan formation.* The alkyl halides react much more readily with potassium bisulfide or sodium bisulfide to form mercaptans than the aryl halides react with these salts to form thiophenols. Experience with many compounds indicates that this test is satisfactory for distinguishing alkyl halides. The odors of the mercaptans are very characteristic for compounds containing less than 8 carbon atoms. The higher mercaptans smell more like the alcohols of similar molecular weight.

Dissolve 200 mg of the halogen compound in 2 ml of ethanol and add this mixture to 2 ml of the bisulfide reagent.[10] Sniff the odor of the solution. If the mercaptan odor is not detected, warm the mixture and sniff it occasionally. Thiophenols are not formed unless the solution is boiled. The odors of the thiophenols are similar to those of the mercaptans.

Compounds Containing Sulfur in the Major Functional Group

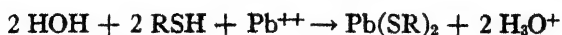
The solubility classification, elemental analysis, and the odor of compounds containing sulfur are all important factors in quickly identifying the class of compound.

6.28 Mercaptans. The low-molecular-weight mercaptans and thiophenols are only slightly soluble in water but dissolve in sodium hydroxide to form salts. Both have penetrating, objectionable odors. The thiophenols are not very common. They may be detected by the test for aromatic structures and by their ease of nitration or bromination. The tests given below are designed particularly for mercaptans.

a. *Isatin test.* Mercaptans give a green color of unknown cause in this test. Alkyl sulfides and hydrogen sulfide do not interfere, since they do not give such colorations.

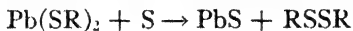
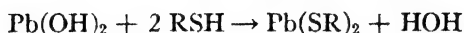
Add 3 drops of a dilute solution of the mercaptan in ethanol to 2 ml of a 1 per cent solution of isatin in concentrated sulfuric acid.

b. *Lead mercaptides.* Mercaptans react with lead or mercuric salts of weak acids to form lead mercaptides or mercuric mercaptides. Lead acetate or mercuric cyanide are generally used for these tests.

$$2\ HOH + 2\ RSH + Pb^{++} \rightarrow Pb(SR)_2 + 2\ H_3O^+$$

Add 2 drops of the mercaptan to 5 ml of a saturated solution of lead acetate in ethanol. Lead mercaptide (yellow) precipitates.

[10] See the Appendix for method of preparation.

c. *Lead sulfide.* The petroleum industry makes extensive use of a so-called *doctor test* for *sour* distillates—that is, those containing mercaptans. With mercaptans, the reagent (sodium plumbite) first forms the yellow lead mercaptides, which are converted by sulfur to the black lead sulfide and the alkyl disulfides. The chemical changes in this test are variable, but one pair of equations may be written as follows:

$$Pb(OH)_2 + 2\ RSH \rightarrow Pb(SR)_2 + HOH$$
$$Pb(SR)_2 + S \rightarrow PbS + RSSR$$

Add 1 drop of a mercaptan to 2 ml of the sodium plumbite solution and shake the mixture vigorously. A yellow precipitate forms. Now add about 50 mg of finely powdered sulfur. The color may first change to orange but will become black within a few minutes.

d. *Nitroprusside.* Mercaptans, in a slightly alkaline solution of sodium nitroprusside, give about the same deep wine color as is given by hydrogen sulfide. The exact composition of the color complex is not known but it is believed to involve a union of the sulfur with the nitroso group of the nitroprusside. Alkyl sulfides (Test 6.30) also react with sodium nitroprusside but the color is more red than blue. Thiophenols also give this test if ammonium hydroxide is substituted for the sodium hydroxide.

Add 1 drop of the mercaptan to 2 ml of a 1 per cent solution of sodium nitroprusside and then add 3 drops of 10 per cent sodium hydroxide. A deep wine color forms. The color changes to yellow if the solution is acidified with hydrochloric acid. Aryl sulfides do not give this test.

6.29 Sulfates. The salts formed by organic bases with sulfuric acid may be decomposed by sodium hydroxide and the base extracted by ether for identification. The sulfate radical may be detected in the aqueous layer by acidifying it and adding barium chloride solution. The alkyl esters of sulfuric acid may be hydrolyzed by refluxing them with 10 per cent hydrochloric acid for 15 minutes and then testing for the sulfate radical with barium chloride.

Caution: *All of the liquid alkyl sulfates are very poisonous. Avoid inhaling the fumes or getting them on the skin.*

Shake 300 mg of the salt with 5 ml of 10 per cent sodium hydroxide. Extract the free base with ether and separate the ether layer. Acidify the aqueous layer with acetic acid and add 3 drops of 5 per cent barium chloride solution. A white precipitate of barium sulfate will form if the compound was an amine sulfate.

6.30 Sulfides. Not only are the sulfides in a different Solubility

Division from the mercaptans but the odors are quite different also. The chemical tests for the two groups are sufficiently similar to be confusing (Test 6.28). If sulfides are used instead of mercaptans in Test 6.28-c, the first precipitate is very light yellow instead of golden yellow. The addition of free sulfur gives an orange color but, unless the compound is hydrolyzed, it does not turn black. If alkyl sulfides are substituted for mercaptans in Test 6.28-d, the color is red rather than wine and tends to become yellow

6.31 Sulfonamides. The sulfonamides may be decomposed by fusing them with solid sodium hydroxide. Ammonia is evolved and may be detected (Test 6.14)

$$C_6H_5SO_2NH_2 + 2\ NaOH \rightarrow C_6H_5ONa + NaHSO_3 + NH_3$$

Acidification of the sulfite will liberate sulfur dioxide, which may be used to oxidize green nickelous hydroxide to the grey-black nickelic hydroxide. Greater accuracy is given to this test for evolved sulfur dioxide by using the nickelic hydroxide to oxidize benzidine acetate to benzidine blue, which is a complex molecule involving the structure $-N=C_6H_4=C_6H_4=N-$. N-substituted sulfonamides will evolve amines instead of ammonia.

Prepare the nickel hydroxide for use in this test by precipitating nickelous chloride with sodium hydroxide and then washing the precipitate until it is alkali-free. The benzidine acetate is prepared by dissolving 50 mg of benzidine in 100 ml of 10 per cent acetic acid. The nickelous hydroxide is applied as a paste to a strip of filter paper. It should be prepared just before it is to be used.

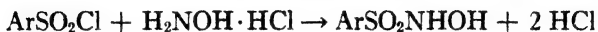
In a Pyrex tube, fuse 0.5 g of the sulfonamide with 3 g of sodium hydroxide. Test the escaping gas for ammonia or volatile amines. When the fusion tube has cooled, dissolve the melt in distilled water. Acidify the solution with hydrochloric acid and suspend a strip of filter paper that has been covered with a paste of nickelous hydroxide over the tube. Warm the tube to hasten the evolution of the sulfur dioxide. A change of color from green to grey-black indicates that the nickelous hydroxide has been oxidized by the sulfur dioxide. Add a drop of benzidine acetate solution to the nickel hydroxide. If oxidation has occurred, the benzidine will turn a bright blue immediately. A blue color that develops only after several minutes should be disregarded.

Many classes of compounds containing oxidized sulfur will evolve sulfur dioxide when fused with sodium hydroxide. Therefore, unless both ammonia and sulfur dioxide are evolved, the compound is not a sulfonamide. A few compounds besides sulfonamides will give both tests, but

they would not be confused with the sulfonamides because of solubility differences.

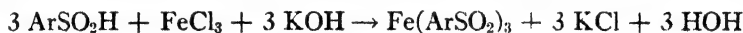
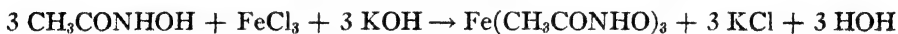
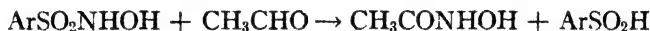
6.32 Sulfonic acids: a. *Hydroxamate test.* Sulfonic acids may be converted to sulfohydroxamic acids by first converting them to the sulfonchloride and then treating with hydroxylamine hydrochloride.

$$ArSO_3H + SOCl_2 \rightarrow ArSO_2Cl + HCl + SO_2$$

$$ArSO_2Cl + H_2NOH \cdot HCl \rightarrow ArSO_2NHOH + 2\ HCl$$

The sulfohydroxamic acids react with acetaldehyde[11] in alkaline solution to form acethydroxamic acid and a sulfinic acid, both of which will react with ferric chloride. The hydroxamic acid reacts with the ferric ion to yield the wine-colored soluble ferric hydroxamate, whereas the sulfinic acid reacts with the ferric ion to yield an orange-red insoluble precipitate.

$$ArSO_2NHOH + CH_3CHO \rightarrow CH_3CONHOH + ArSO_2H$$

$$3\ CH_3CONHOH + FeCl_3 + 3\ KOH \rightarrow Fe(CH_3CONHO)_3 + 3\ KCl + 3\ HOH$$

$$3\ ArSO_2H + FeCl_3 + 3\ KOH \rightarrow Fe(ArSO_2)_3 + 3\ KCl + 3\ HOH$$

The salts of sulfonic acids may be treated by this method by first neutralizing the salt with hydrochloric acid and then evaporating the solution to dryness before treating with thionyl chloride.

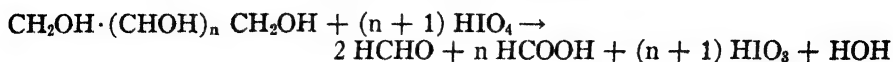
Add 5 drops of thionyl chloride to 100 mg of the sulfonic acid in a test tube and place the tube in boiling water for 1 minute. Cool the tube and add 0.5 ml of a methanol solution of hydroxylamine hydrochloride and 1 drop of acetaldehyde. Make the solution alkaline by adding 2 *N* potassium hydroxide (in methanol). Heat the mixture just to boiling and then cool it. Acidify the mixture with dilute hydrochloric acid and add a drop of 5 per cent ferric chloride. A wine coloration, with or without a brown-red precipitate, is a positive test for a sulfonic acid.

b. *Fusion test.* Sulfonic acids, sulfinic acids, and sulfones all liberate sulfur dioxide when fused with sodium hydroxide by the method given in Test 6.31. The sulfonic and sulfinic acids may be distinguished from the sulfones by solubility differences and by the acidity of their solutions. If sulfides are present, black nickel sulfide will be formed when Test 6.31 is performed.

Miscellaneous Tests

6.33 Polyhydroxy compounds. Most polyhydroxy alcohols and many carbohydrates may be decomposed by cold periodic acid to formaldehyde, formic acid, and water according to the equation:[12]

[11] Feigl, *Spot Tests*, Nordeman Pub. Co., New York, 1939, p. 303.
[12] Feigl, *op. cit.*, p. 272.

$$CH_2OH \cdot (CHOH)_n\ CH_2OH + (n + 1)\ HIO_4 \rightarrow 2\ HCHO + n\ HCOOH + (n + 1)\ HIO_3 + HOH$$

The formaldehyde resulting from this decomposition may be detected by the Schiff test (Test 6.5-b). Aldehydes must be proved absent before making this test. Tartaric acid will give a positive test but citric acid is negative.

Iodic acid, which is formed in this reaction, is capable of oxidizing low-molecular-weight alcohols, aldehydes, methylketones, phenols, and aniline derivatives.[13] The iodic acid is reduced to hydroiodic acid and these two acids react to form iodine. Hence the brown color of free iodine may develop during this test.

Add 1 drop of a 5–10 per cent solution of the polyhydroxy alcohol in water or alcohol to 1 drop of a 5 per cent aqueous solution of potassium periodate and then add 1 drop of 1 *N* sulfuric acid. Allow the mixture to stand for 5 minutes and then add 3 drops of a saturated solution of sulfurous acid to reduce the excess potassium iodate. Add 1 drop of Schiff's reagent and allow the mixture to stand. The characteristic red-blue color will develop in half an hour at the longest. Polysaccharides give the test if the mixture is heated to boiling before adding the Schiff's reagent.

6.34 Additional color tests. The chemical literature records many reagents that produce colors with one or more classes of compounds. In addition to those that have been used in this chapter, the reader may desire to consult the literature for additional color tests, a few of which are listed below.

a. *Concentrated sulfuric acid.* Cold concentrated sulfuric acid produces a variety of colors with many compounds, particularly with those that are polycyclic or highly substituted.[14] Since the reactions do not occur for all the members of any one major chemical class, they are not satisfactory in general classification tests but are frequently valuable in helping to identify a particular compound.

Compounds may give a coloration in warm or hot concentrated sulfuric acid when they fail to color the cold acid. Some compounds show different colors in the cold and hot acid. A large number of compounds from several classes will be charred by the acid and hence show tan, brown, or black colors. This occurs most frequently with cyclic compounds and the carbohydrates. Compounds containing iodine generally turn the hot acid to a purple color.

[13] Williams and Woods, *J. Am. Chem. Soc.*, **59**, 1408 (1937).

[14] Campbell, *Qualitative Organic Chemistry*, The Macmillan Co., London, 1939, p. 44; also published by D. Van Nostrand, New York, 1939.

b. *Ferric chloride.* The ferric chloride test for phenols has been used in this chapter. The actual colors given by about seventy-five such compounds have been published.[15]

c. *Sodium pentacyano-ammine-ferroate.* This reagent gives a variety of colors with nitro and nitroso compounds, hydrazines, thioketones, α-β unsaturated aldehydes, and aromatic aldehydes.[16] The methods of testing and the colors produced for many individual compounds for this reagent, and also for those referred to in the next five tests, have been included in a recent book.[17]

d. *Fluorescein chloride.* This reagent gives colors with amines, amides, nitriles, and pyrole derivatives.[18]

e. *1,2-naphthaquinone-4-sulfonate.* Compounds containing reactive methylene or amino groups give color reactions with this reagent. Tertiary ring bases may be detected by the same reagent by first combining them with methyl iodide.[19]

f. *o-Dianisidine.* This is one of the many reagents that have been suggested for aldehydes.[20]

g. *Primary aromatic amines.* Two of the reagents used to produce colors with primary aromatic amines are glutaconic aldehyde[21] and sodium pentacyano-aquo-ferriate.[22]

h. *m-Dinitrocompounds.* The *meta* dinitrocompounds react with potassium cyanide to give colors that distinguish them from the isomeric *o-* or *p-* compounds.[23]

6.35 Hydrolysis. Several classes of compounds may best be identified by hydrolyzing them to one or two products that may be more readily identified than the original compound. The hydrolysis of nitriles, amides, substituted amides, hydrazones, semicarbazones, and esters has been discussed in preceding tests. Ethers may also be hydrolyzed. Most of these compounds must be hydrolyzed before derivatives can be prepared to prove their identity (see Procedures 10.16–10.18, pages 236-240).

6.36 Iodoform test. Many compounds that contain the structure CH_3CO, or that can be readily oxidized to contain this structure, may be converted to iodoform by an alkaline solution of sodium hypoiodite.[24] Com-

[15] Wesp and Brode, *J. Am. Chem Soc*, **56**, 1037 (1934)
[16] Feigl, Anger, and Frehden, *Mikrochemie*, **15**, 183 (1934).
[17] Feigl, *op. cit.*
[18] Feigl, Anger, and Zappert, *Mikrochemie*, **16**, 70 (1934).
[19] Feigl and Frehden, *Mikrochemie*, **16**, 79 and 84 (1934).
[20] Wasicky and Frehden, *Mikrochim. Acta*, **1**, 55 (1937).
[21] Fretag and Neudert, *J. prakt Chem.*, 135, (2), 180 (1932)
[22] Anger, *Mikrochim. Acta*, **2**, 3 (1937).
[23] *Ibid.*, **2**, 6 (1937)
[24] Fuson and Bull, *Chem. Rev*, **16**, 275 (1934).

pounds do not give the test if the CH_3CO group that is present is converted to acetic acid as a result of hydrolyzing the molecule—*e.g.*, aceto acetic acid. The test is given by ethanol, acetaldehyde, methyl ketones, and by those secondary alcohols that yield methyl ketones on oxidation. For acetaldehyde, the equation is:

$$CH_3CHO + 4\ NaOH + 3\ I_2 \rightarrow CHI_3 + 3\ HOH + HCOONa + 3\ NaI$$

Dissolve 100 mg of the compound being tested in 1 ml of water (use dioxane if the compound is insoluble in water). Add 3 ml of 10 per cent sodium hydroxide solution and then add dropwise a 10 per cent solution of iodine in a 20 per cent solution of potassium iodide in water, until a slight excess of iodine exists in the solution. Place the tube in a beaker of 60° water. Add more iodine until the iodine color persists for 2 minutes and then add drops of 10 per cent sodium hydroxide solution until the brown iodine color just disappears. Remove the tube from the warm water and add 10 ml of water. Iodoform precipitates as a yellow solid, which melts at 120°.

6.37 Agents for oxidation. A large number of oxidizing agents are used in organic laboratory work. A few of the more common cases omitted in this chapter are: (1) a mixture of potassium dichromate and sulfuric acid, which is often chosen when oxidizing alcohols; (2) a mixture of potassium permanganate and sodium carbonate, which is generally used to split a molecule at a noncyclic double-bond, or to oxidize an alkyl side-chain to a carboxyl group; (3) an alkaline solution of picric acid, which is used qualitatively, and may also be used quantitatively in colorimetric analysis (the yellow picrate ion is reduced to the amber-red picramate ion); and (4) Benedict's quantitative reagent used in the estimation of reducing sugars. For a discussion of oxidation as a method of preparing derivatives, see pages 171–176.

Generally useful oxidizing agents are given below.

a. *Cupric ion.* Several solutions using cupric ion as the oxidizing agent have been named after the men who proposed them. They differ as regards the pH of the solution and the salts used to prevent the precipitation of the copper ions.

(1) *Benedict's reagent.* Benedict's qualitative reagent[25] differs from Fehling's reagent in that it is less alkaline. (Consult the Appendix for the relative compositions.) It has an advantage over Fehling's reagent in that it may be stocked as one solution, whereas Fehling's reagent must be prepared from two solutions at the time it is used. The precipitate from both Benedict's and Fehling's reagents is cuprous oxide, the color

[25] Benedict, *J. Biol. Chem.*, **3**, 101 (1907), and **5**, 485 (1908).

of which depends on the particle size and varies from bluish-green for the very finely divided oxide to a red for the largest particles; most commonly it is yellow-orange. It should be remembered that a yellow suspension in the blue reagent will make the mixture appear green.

Add 50 mg of the compound to 1 ml of Benedict's qualitative reagent and immerse the tube in boiling water for 5 minutes. If the compound is easily oxidized, a yellow, orange, or red precipitate will form.

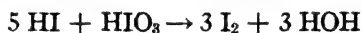
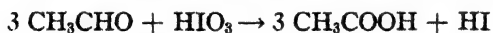
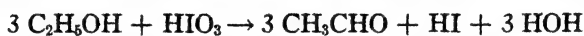
(2) *Fehling's reagent.*[26] Mix 1 ml of Fehling's solution "A" with 1 ml of solution "B" and shake the mixture until a clear solution results. Add 50 mg of the compound being tested and boil the mixture gently for 2 minutes. The precipitation of cuprous oxide is a positive test for an easily oxidized compound.

b. *Iodic acid.* It has been found[27] that iodic acid is a selective oxidizing agent. The following are oxidized by iodic acid under the conditions specified: Simple alcohols up to heptanol (except methanol), aldehydes, methyl ketones, phenols, and aniline derivatives. The following are not oxidized: polyhydroxy alcohols (except 1, 2 and 1, 3 propandiol), acids, and sugars (except fructose and sucrose).

Using ethanol as the compound, the equations for this test are:

$$3\ C_2H_5OH + HIO_3 \rightarrow 3\ CH_3CHO + HI + 3\ HOH$$

$$3\ CH_3CHO + HIO_3 \rightarrow 3\ CH_3COOH + HI$$

$$5\ HI + HIO_3 \rightarrow 3\ I_2 + 3\ HOH$$

The reagent is prepared by carefully adding 2.5 ml of concentrated sulfuric acid to 8 ml of water, cooling the mixture to room temperature, and adding 100 mg of potassium iodate. To this reagent, add 50 mg of the compound and keep the tube immersed in boiling water for an hour, unless oxidation occurs more quickly. A brown color due to suspended iodine is a positive test.

c. *Silver ion: Tollen's reagent.* This reagent is an alkaline solution containing silver-ammonia complex ions. The silver ion is reduced to metallic silver by most aldehydes, readily oxidized sugars, polyhydroxy phenols, amino phenols, hydroxylamine, and other reducing agents.[28]

Boil 5 ml of 10 per cent sodium hydroxide solution in a test tube for 1 minute to clean the tube thoroughly. Discard the solution and use the tube in the following test. The silver will generally plate out on the tube. A black precipitate of metallic silver is, however, an equally positive test. The reagent is prepared just before use by adding 0.5 ml of 10 per cent

[26] Herstein, *J. Am. Chem. Soc.*, **32**, 779 (1910).
[27] Williams and Woods, *J. Am. Chem. Soc.*, **59**, 1408 (1937).
[28] Morgan and Mickelwait, *J. Soc. Chem. Ind.*, **21**, 1375 (1902).

aqueous sodium hydroxide to 1 ml of a 5 per cent solution of silver nitrate in dilute ammonia (half-concentrated ammonium hydroxide and half water). Shake the tube. If a precipitate exists, add dilute ammonia dropwise (while shaking the tube) until the precipitate dissolves.

Add 50 mg of the compound to be tested to the freshly mixed Tollen's reagent. Do not heat the mixture; rather, allow it to stand for 10 minutes. A precipitate of silver is a positive test.

As soon as the test is completed, pour the mixture down the sink and wash it down.

6.38 Picric acid as a reagent. Picric acid is a versatile reagent. It forms addition compounds with aromatic hydrocarbons, phenols, and phenolic ethers; picrates with amines, many amino acids, hydrazines, thioureas, and alkaloids (see pages 193, 264, and 281); and acts as an oxidizing agent on easily oxidized compounds such as reducing sugars, aliphatic aldehydes, methyl ketones, hydrazines, and polyhydroxy phenols. It is reported[29] that any compound containing a CH, CH_2, or CH_3 group contiguous to negative groups such as CHO, CO, NO_2, or CN will give the amber-red coloration characteristic of the reduction of alkaline picrate solutions.

a. *Molecular compounds:* (1) *Aromatic hydrocarbons.* The picrates of benzene, toluene, ethyl and propyl benzene, and the xylenes are unstable and extremely difficult to prepare. The picrates of the other aromatic hydrocarbons may be prepared by either the solvent method or the fusion method.[30] To use the solvent method, prepare separate saturated solutions (2–3 ml of each) of the hydrocarbon and picric acid in ethanol. Mix these two solutions in quantities so that equal molecular weights of the hydrocarbon and picric acid will be present (one millimole of each is sufficient). Heat the mixture to boiling and allow it to cool. The picrate crystals are yellow, orange, or red.

The fusion method consists of mixing equal molecular quantities of the dry hydrocarbon and dry picric acid and heating the mixture to the fusion point. The mass is then recrystallized (generally from ethanol).

(2) *Phenols.* Picrates of many phenols have been prepared by the fusion method given for hydrocarbons.

(3) *Phenolic ethers.* The colors and melting points for thirty-five picrates of phenolic ethers are on record.[31]

Dissolve 1 millimole of the phenolic ether in the minimum amount of boiling chloroform. Similarly prepare a saturated solution of 1 milli-

[29] Goswami, Shaha, and Mukerjee, *J. Indian Chem. Soc.*, **11**, 773 (1934).
[30] Baril and Hauber, *J. Am. Chem. Soc.*, **53**, 1087 (1931).
[31] Baril and Megrdichian, *J. Am. Chem. Soc.*, **58**, 1415 (1936).

mole of picric acid in boiling chloroform. Mix the two solutions and allow the mixture to stand for crystallization.

b. *Picrate salts.* The picrate salts of basic compounds[32] are prepared by mixing saturated hot solutions containing a slight excess of picric acid and allowing the mixtures to cool. Water, dilute ethanol, ethanol, 10 per cent acetic acid, and benzene are recommended (in that order) as solvents.

c. *Picric acid as an oxidizing agent.* Place a test tube containing 2 ml of a saturated aqueous solution of picric acid in a bath of boiling water. Add 1 ml of 5 per cent sodium hydroxide solution and 50 mg of the compound to be tested. Keep the tube in the water-bath for 30 minutes unless a reaction occurs more quickly. If necessary, add water to the tube to replace water lost by evaporation. A positive test is evidenced by the yellow color of the picrate ion, changing to the red color of the picramate ion. This involves the reduction of one nitro group to an amino group.

[32] Mulliken-Huntress, *Manual of the Identification of Organic Compounds,* M. I. T. Bookstore, Cambridge, Mass., 1937, p. 157.

Selection of the Probable Compound

ONE purpose of this chapter is to show how the data collected about an unknown, in accordance with the directions of the first six chapters, may be coordinated to make it possible to select the *probable* identity of the compound. Another purpose is to point the way to the further steps that must be taken to *prove* the identity of the compound.

Anyone who has followed this text systematically has taken the first two of the four steps indicated here in the identification of an unknown and in the proof of its identity. He is now ready to take the third step. The fourth step must be taken as a part of the final proof.

1. The compound, if impure, is purified.
   a. At least one physical constant is determined and recorded.
2. The chemical class of the compound is determined by:
   a. Gross examination.
   b. Analysis for the elements present.
   c. Classification into a Solubility Division.
   d. Identification of the functional groups present.
3. The collected data are coordinated and a list prepared of the compounds that approximately fit the data for the unknown.
4. The compound is finally identified by preparing derivatives.

Interpretation of the classification data. The data given below are similar to those that would be collected by an investigator working with an unknown in the laboratory. In the case of the first two examples, the beginner should try to deduce the *probable* identity of the compound from the data given in the first paragraph before he reads the interpretations given in the second paragraph.

Example 1. The unknown is a colorless solid melting at 94°. It burns with a smoky flame but does not leave a residue. It does not decolorize a solution of permanganate, but does decolorize rather readily a solution of bromine in carbon tetrachloride. The benzenoid structure test with aluminum chloride (page 87) gives a purple color. On analysis, iodine is found present but no nitrogen or sulfur. The compound is classified in Solubility Division *A*. It gives negative results with Tests 5.6-a and 5.6-d (page 118) and gives purple colorations with both 5.6-b and 5.6-c. It gives negative results with Test 6.11-a (page 128) but positive tests

with 6.11-b and 6.11-c. With Test 6.27-a (page 139) the solution becomes slightly cloudy but no precipitate forms. Test 6.27-b gives a very slight, cream-colored precipitate.

The fact that the compound burns with a smoky flame indicates a high ratio of carbon with respect to oxygen and hydrogen (probably an aromatic compound). The absence of an ash shows that it does not contain a metal. Failure to decolorize permanganate solution indicates that the compound does not contain active unsaturated linkages or other easily oxidized groups. The fact that it reacts with bromine even though it did not react with permanganate indicates that it is a substituted aromatic compound that is easily brominated. The purple color formed on the aluminum chloride indicates a polycyclic compound but, when it is found that iodine is present, it is recalled that iodine containing compounds decomposes during this test to give purple colors whether or not the compound is cyclic. Since the other data also indicated a cyclic structure, the compound may still be presumed to be cyclic, but not necessarily polycyclic. Because it falls in Solubility Division *A* and contains iodine, it is most likely an iodine-substituted acid or phenol. Test 5.6 applies to phenols but not to acids. The fact that the "b" and "c" parts of Test 5.6 are positive strongly indicates that the unknown is a phenol, since the other hydroxy compounds, such as alcohols, are ruled out by the solubility classification. The negative results on Test 5.6-a may be explained by the insolubility of the unknown in water. Test 5.6-d is not applicable to phenols. Failure of the unknown to give positive results with Test 6.11-a is explainable if the *para* position with respect to the hydroxyl group is occupied. Since the unknown contains iodine, that atom might be *para* to the hydroxyl group. The slight reactivity of the iodine as shown by the results of Test 6.27 is further indication that the unknown is cyclic, since the iodine is acting like an aryl iodide rather than the more reactive alkyl iodides. The conclusion, then, is that the unknown is a *p*-iodophenol. Since the melting point of the unknown is 94°, it is probable that the compound is *p*-iodophenol.

Example 2. The unknown is a solid with explosive tendencies during ignition. It melts at 178–179°, contains nitrogen but no halogen or sulfur, and is in Solubility Division *M*. Negative results are obtained with Tests 6.13, 6.14, 6.15, and 6.16-a, b, and c (pages 129–131). Positive results are obtained with Tests 6.16-d, f; 6.18; 6.19; and 6.20 (red color).

The Division *M* compounds should always be tested for all possible functional groups. The important discovery with this unknown is that it gives a positive reaction with Test 6.16-d, thus indicating that it is a primary arylamine. This reaction is unexpected, since the unknown

failed to dissolve in 10 per cent hydrochloric acid. However, it is recalled that many *ortho-*, or *ortho-* and *para-*, substituted arylamines fail to dissolve in dilute acids. Tests 6.16-f, 6.18 and 6.19 indicate the presence of nitro groups. Test 6.20 shows that the compound contains three nitro groups, or, as one of the exceptions, it might be 2, 4-dinitroaniline. The latter compound would exactly meet the specifications of the data collected, including the melting point.

Example 3. The unknown is a Division *A* solid containing bromine, nitrogen, and sulfur and melts at 166°. It is aromatic and the bromine is only slightly active. Because of the elements found present and the solubility, Test 6.31 (page 142) is made before any other tests for groups containing nitrogen or sulfur. Both ammonia and sulfur dioxide are evolved during this test. When the fusion residue is acidified, an oily liquid separates from the aqueous solution and proves to be bromobenzene. What is the unknown?

Selecting the probable compound. After the chemical class to which an unknown belongs has been determined with reasonable certainty, there remains the problem of deciding which particular member of the class it is. To do this, note the melting point or boiling of the pure compound and then consult the table that lists the particular class desired. Locate the compounds in the class for which the physical constant is within 3 degrees of that found for the unknown and make a list of them. The determination of the refractive index (see page 63) may be worth while at this point if the substance is a liquid. Unless the unknown is a compound not listed in the table of this text (which is not very probable), it should be some one of those compounds. It will often happen that some of these "possibilities" may be eliminated by the elements present, or by performing *spot tests* that are specific for certain ones of them and comparing the results with similar tests on the unknown. For example, if the unknown is a chlorine-substituted alcohol boiling at 127°–128°, only 2 of the 7 alcohols boiling between 124.5° and 132° need be considered, since the other 5 do not contain chlorine. If the unknown is an acid boiling at 139°–140°, it might be either acrylic acid or propionic acid. Since acrylic acid is unsaturated and propionic acid is saturated, the results of the saturation test on the unknown would settle the matter.

Selecting the derivative. The final decision as to the identity of an unknown should be reserved until one or more derivatives have been prepared whose melting points correspond to those recorded in the tables for the derivatives of the compound that the unknown is believed to be. If it is possible to make a *mixed melting-point* determination of the unknown with the compound it is believed to be, this data and the data on

one derivative are considered by many chemists as equivalent to the data from two derivatives. (For apparatus to make a mixed melting-point determination on low-melting compounds, see Figure 18, page 37).

To illustrate, let it be assumed that an organic liquid is under investigation. It boils between 135° and 155° and about 80 per cent of it between 140° and 143°. The liquid has a pungent odor. Elementary analysis shows the presence of carbon and hydrogen. The liquid is soluble in water and in ether and its aqueous solution has acidic properties. On the basis of these data a list of possible carboxylic acids is made by referring to Table 1, page 358; acrylic b.p. 140°; propionic b.p. 141°; propiolic b.p. 144°; isobutyric b.p. 155°.

Since the original liquid does not decolorize permanganate or bromine solutions rapidly, the possibility of acrylic or propiolic acid is tentatively excluded. Therefore the two remaining possibilities are propionic and isobutyric acids, with the boiling point data indicating that the unknown is most likely impure propionic acid. Thus, the final and conclusive step for the proof of this tentative assumption is to prepare a suitable derivative from that fraction of the liquid which boils at 140–143° or preferably from a fraction that boils at 140–142°. If the derivative prepared melts within 1–2° of the melting point given in the literature (Table 1) for the same derivative of propionic acid, the evidence for the assumption that the unknown is impure propionic acid is strengthened. If another derivative is prepared and is also found to melt within 1° of the melting point given in the literature for the same derivative of propionic acid the proof is more complete. Finally, if a mixture consisting of the derivative prepared from the unknown and the same derivative prepared from pure propionic acid melts without showing a variation of more than 1° from the melting point of either component alone, then the proof is considered conclusive.

Notice what derivatives are recommended for the compounds in the possible list among which the unknown is being sought. Determine whether or not the physical constants listed for the compounds under consideration are sufficiently different to make identification definite. For example, there would be no point in preparing the anilide to distinguish propionic acid from isobutyric acid since these anilides melt at about the same temperature. The *p*-toluidides would be satisfactory since they melt 17° apart.

Select the derivatives that appear best suited and consult the following chapters for methods of preparing them.

In order to become acquainted with the procedure, it is wise for beginners to select a compound believed to be similar to the unknown and

use it for the preparation of derivatives by the chosen methods before the unknown itself is used. In making a derivative from a known compound, use the small quantities commonly used for an unknown.

If the compound being examined is an acid or an anhydride, the *neutral equivalent* may be determined. Esters have *saponification equivalents*, and many of the naturally occurring esters (that is, drying oils and edible oils) have *iodine numbers* that aid in their identification. Procedures for determining neutral equivalents, saponification equivalents, and iodine numbers are given in the Appendix, pages 469–471.

Use of the library. It must be apparent to the reader that this text is neither an all-inclusive treatise on tests and derivatives for the very large number of organic compounds nor a compendium of methods for every possible situation. For example, the Raman spectra method for the identification of the paraffin hydrocarbons,[1] the Quense and Dehn microscopic method for identifying sugars and polyhydric alcohols,[2] and the general spectographic and microscopic methods are not included in this text. It is necessary, therefore, to consult frequently more complete listings of organic compounds, derivatives, specific tests, and other identification data. The section on organic chemistry in Soule's *Library Guide for the Chemist* (McGraw-Hill) discusses the major source materials and how to use them. Attention is called to the fact that a large number of references to the literature is given in connection with the various chapters of this text; the following works will also be found useful.

Selected References on Organic Chemistry

Beilsteins Handbuch der organischen Chemie, 4th ed., J. Springer, Berlin, 1918–42. Consists of 27 volumes containing literature up to 1909, and 27 supplementary volumes up to 1919 complete, also the first 4 second supplementary volumes (on aliphatic compounds only) up to 1929 inclusive, together with a General Subject Index (in 2 parts) and a General Formula Index (in 2 parts) constituting vols. 28 and 29, as well as vol. 30 on natural substances (rubber, etc.) (only 121 pp.) and vol. 31 on natural substances (carbohydrates, part I. Monosaccharides and Oligosaccharides, up to Tetrasaccharides).

Beilsteins Handbuch gives, so far as recorded in the literature, concise particulars on the following topics: *Historical; occurrence; formation;* methods of *preparation;* physical properties (including generalities on salt formation). *Chemical behavior* (under heat, electricity, oxidation, reduction, halogenation, etc., inorganic reagents, and reactions with other organic compounds). *Bio-*

[1] Grosse, Rosenbaum and Jacobson, *Ind. Eng. Chem., Anal. Ed.*, **12**, 191 (1940).
[2] Quense and Dehn, *ibid.*, **11**, 555 (1939); *ibid.*, **12**, 556 (1940).

chemical behavior; Uses; Analytical (identification, purity tests, quant. determination, etc.) Addition compounds and salts.

As guides to the consultation of this great work there are available:

1. *System der organischen Verbindungen: ein Leitfaden fur die Benutzung von Beilsteins Handbuch der organischen Chemie*, by B. Prager, et al., J. Springer, Berlin, 1929 (246 pp.). This book is not an index, but gives the system of classification and the system numbers of groups of compounds employed in *Beilsteins Handbuch.*

2. *Kurze Anleitung zur Orientierung in Beilsteins Handbuch der organischen Chemie*, by F. Richter, J. Springer, Berlin, 1936 (23 pp.). Affords a summary view of the division by functional groups, etc.

3. E. H. Huntress' *Brief Introduction to the Use of Beilstein*, John Wiley & Sons, Inc., New York, 1938. Provides a very helpful guide in English.

Heilbron's *Dictionary of Organic Compounds*, in 3 vols. Oxford University Press, New York, 1943. This is the most complete catalog of organic compounds in the English language. Contains the formula, physical data, and characteristic reactions of thousands of compounds, together with the melting point of identification derivatives, with references (which, however, are not usually given in connection with the data and are therefore not very helpful).

Chemical Abstracts, published by the American Chemical Society, Washington, D. C. Beginning with the year 1907 up to date. Contains abstracts of chemical literature with formula and author indexes. Decennial Indexes, 1917 1926, Vols. 11-20, 1927 1936, Vols. 21–30.

Chemisches Zentralblatt (last publisher, Verlag Chemie, Berlin). Beginning with the year 1830 up to date. Contains abstracts of chemical literature like those in *Chemical Abstracts*, with formula indexes from 1922 on.

M. M. Richter, *Lexikon der Kohlenstoff-Verbindungen*, 3rd ed., L. Voss, Leipzig, 1910–2 (4751 pp.). Lists all organic compounds known up to 1910, arranged according to formulas and giving one or more literature references for each, but no properties except melting point or boiling point.

The above work is continued in R. Stelzner, *Literatur Register der Organischen Chemie*, F. Vieweg & Son, Braunschweig, 1913, and Verlag Chemie, Berlin, 1926, in 5 volumes.

E. Abderhalden, *Biochemisches Handlexikon*, J. Springer, Berlin, 1910– of which 15 volumes have been published. Contains much information and numerous references on amino acids and other chemical compounds of a biochemical nature.

E. Abderhalden, *Handbuch der biologischen Arbeitsmethoden*, Urban & Schwarzenberg, Berlin, 1920–1939. Consists of 106 large volumes, which contain detailed directions for halogenation, dehalogenation, etc. An index to these books has been issued under the title *Gesamtinhaltsübersicht, Stichwort- und Mitarbeiterverzeichnis*, by the same publishers (324 pp.).

Allen's Commercial Organic Analysis, 5th Ed., P. Blakiston's Son and Co., Philadelphia, Pa., 1923–1933. In 10 volumes, which cover the identification,

separation, and quantitative estimation of the most important commercial organic products.

International Critical Tables of Numerical Data, Physics, Chemistry, and Technology, prepared by the International Research Council, McGraw-Hill Book Co., Inc., New York, 1926-1933, in 7 volumes and an Index.

A. B. Prescott, *Outlines of Proximate Organic Analysis*, 4th Ed., D. Van Nostrand Co., New York, 1893 (192 pp.). Covers identification, separation, and quantitative determination of the more commonly occurring organic compounds, such as succinic acid, lactose, and the like.

For consultation on works that provide methods for the identification of organic compounds, specific tests, color tests, derivatives, and other pertinent data the reader is referred to:

S. P. Mulliken, *The Identification of Pure Organic Compounds* (in 4 vols.), John Wiley and Sons, Inc., New York, 1904–1922. Gives data and derivatives for identification of a large number of compounds.

C. H. Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds* (Vol. I containing compounds of carbon with hydrogen or with hydrogen and oxygen), John Wiley and Sons, Inc., New York, 1941.

R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 2nd Ed., John Wiley and Sons, New York, 1940 (312 pp.).

S. M. McElvain, *Characterization of Organic Compounds*, Macmillan, New York, 1945.

O. Kamm, *Qualitative Organic Analysis*, John Wiley and Sons, Inc., New York, 1922.

N. Campbell, *Qualitative Organic Chemistry*, D. Van Nostrand Co., New York, 1939. Largely devoted to identification characteristics and derivatives.

H. T. Clarke, *Handbook of Organic Analysis*, 4th Ed., Arnold, London, 1926.

Organic Reagents for Organic Analysis by Staff of Hopkins & Williams Research Laboratory, Chemical Publishing Co., New York, 1946 (175 pp.).

H. Middleton, *Systematic Qualitative Organic Analysis*, 2nd Ed., Arnold & Co., London, 1943.

L. Ekkert, *Erkennung organischer Verbindung im besonderen von Arzneimitteln*, F. Enke, Stuttgart, 1933.

H. J. L. Meyer, *Nachweis und Bestimmung organischer Verbindungen*, J. Springer, Berlin, 1933.

L. Rosenthaler, *Der Nachweis organischer Verbindungen*, 2nd Ed., F. Enke, Stuttgart, 1923 (1028 pp.).

N. Schoorl, *Organische Analyse* (in Dutch), 2nd Ed., Amsterdam, 1921 (160 pp.).

R. Kempf & F. Kutter, *Schmelzpunkt. Tabellen zur Organischen Molekular-Analyse* (1928), (766 pp.). Photostatic reproduction, Edwards Brothers, Ann Arbor, Michigan, 1944.

F. Feigl, *Specific and Special Reactions for Use in Qualitative Analysis*, Elsevier Publishing Company, Inc., New York, 1940.

F. Feigl, *Laboratory Manual of Spot Tests*, Academic Press Inc., New York, 1943.

The two following handbooks list a large number of organic compounds with some of their physical constants:

C. D. Hodgman and H. N. Holmes, *Handbook of Chemistry and Physics*, 29th Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1945.

N. A. Lange, *Handbook of Chemistry*, 6th Ed., Handbook Publisher, Inc., Sandusky, Ohio, 1946.

Extensive bibliographies are to be found in the chapters on derivatives at the end of each section dealing with groups of organic compounds, as for example Acids, Hydroxy Compounds, Amines, etc. The following texts, however, may be listed for general references:

P. S. Arup and J. C. Irvine, *Industrial Organic Analysis*, London, 1913 (340 pp.). Gives directions for analysis of coal and its distillation products, fatty matter, soap, petroleum products, milk, butter, starch, food preservatives, and coloring matters.

Association of Official Agricultural Chemists, *Official and Tentative Methods of Analysis*, 5th Ed., Washington, D. C., 1940 (757 pp.). An excellent work on foods, fertilizers, insecticides, etc.

A. L. & K. B. Winton, *The Analysis of Foods*, John Wiley & Sons, Inc., New York, 1945 (999 pp.). An excellent book in regard to determination of food constituents and color reactions.

C. T. Barfoed, *Lehrbuch der organischen qualitativen Analyse*, Kopenhagen, 1881 (522 pp.). An older book describing properties and analytical reactions of organic acids, neutral substances (like dextrine, resins, oils), and alkaloids.

E. Berl, *Chemisch-technische Untersuchungsmethoden*, J. Springer, 1931–4, Berlin (5 vols.) and supplement, 1939–40 (3 vols.); photolithoprint reproduction by Edwards Brothers, Ann Arbor, Michigan, 1943.

K. H. Bauer, *Analytische Chemie der Alkaloide*, Gebr. Borntraeger, Berlin, 1921 (425 pp.). An excellent book for identification and determination of alkaloids.

J. Formanek, *Untersuchung und Nachweis organischer Farbstoffe auf Spektroskopischem Wege*, J. Springer, Berlin, 1908–11 (2 vols.).

L. Zechmeister and L. Cholnoky, *Principles and Practice of Chromatography*, J. Wiley & Sons, Inc., New York, 1941 (362 pp.).

H. H. Strain, *Chromatographic Adsorption Analysis*, Interscience Publishers, Inc., New York, 1942.

F. Welcher, *Chemical Solutions*, Van Nostrand Co., Ne[illegible] 1942 (404 pp.). Describes preparation and use of many reagents use[illegible]her organic or inorganic analysis.

Solving problems. Chapter 16 consists of problems, the solution of which affords an interesting review of organic reactions and a method of acquiring skill in the use of the tables of this text.

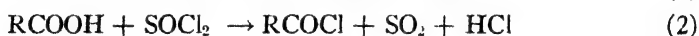
CHAPTER 8

Important Organic Reactions

The preparation of derivatives, which comprises the final step in the identification of an organic compound, requires that the substance under investigation be reacted with a known compound called the *reagent*. If, for example, the unknown compound has been tentatively identified as a lower carboxylic acid, its anilide or *p*-toluidide may be made by one or the other of the two methods illustrated by the following equations:

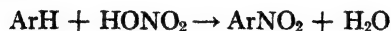
$$RCOOH + R'NH_2 \rightarrow RCONHR' + H_2O \quad (1)$$

$$RCOOH + SOCl_2 \rightarrow RCOCl + SO_2 + HCl \quad (2)$$

$$RCOCl + R'NH_2 \rightarrow RCONHR' + HCl \quad (3)$$

Equation (1) represents the direct reaction of an arylamine with a carboxylic acid. The method indicated by Equations (2) and (3) involves conversion of the acid to the acyl chloride by treatment with thionyl chloride followed by reaction of the acyl halide with the arylamine.

It is obvious that, for the preparation of derivatives, not only is an extensive knowledge of organic reactions required, but also of the practical methods used in the laboratory to carry them out. Although it is assumed that the beginner possesses some elementary knowledge of organic reactions, it has been deemed prudent to include in this book a summary of the most useful organic reactions relating to the preparation of derivatives. Practical directions for preparing the derivatives recommended for each class of compounds are given in Chapters 9–13. In the present chapter the reader will find a brief discussion of the most important organic reactions and their practical applications to semimicro quantities.

Nitration. Substitution of nitro groups in place of hydrogen atoms by the use of nitric acid as the nitrating agent is feasible in dealing with aromatic compounds:

$$ArH + HONO_2 \rightarrow ArNO_2 + H_2O$$

Most aryl nitro compounds are easily prepared by the action of a mixture of nitric and sulfuric acids at 50–60°. If nitration is difficult, a mixture of potassium nitrate and sulfuric acid is employed; in other cases, such as arise in introducing a second nitro group, a mixture of fuming nitric and concentrated or fuming sulfuric acids is used. One of the functions of sulfuric acid in nitrations is to prevent dilution of nitric acid by

absorbing the water formed. Another useful purpose is its solvent action on many organic compounds. In some cases the first action of sulfuric acid is to sulfonate, the sulfonic acid groups being subsequently replaced by nitro groups. Because of their insolubility in water, nitro compounds are rather easily separated by mere dilution of the nitrated mixture. The following preparations illustrate the general methods used. Procedure 8.1 is intended for the preparation of mononitro derivatives and Procedure 8.2 for dinitro derivatives. A more extensive discussion of nitration will be found on pages 284–7, 309, and 313–5.

8.1 Nitronaphthalene. Place in a 6-inch test tube 0.5 ml (about 20 drops) each of concentrated sulfuric and nitric acids. Cool the mixture to room temperature and add, in two portions, 300 mg of naphthalene. Shake after each addition, keeping the temperature below 50° by immersing the tube in cold water. When all the naphthalene has been added, place the tube in a beaker containing water at 50–60° and allow to stand for 5–10 minutes with frequent shaking. Cool and add cautiously 6 ml of ice-cold water. Cool for a few minutes and then pour out the acid mixture, but retain the crystals in the tube by placing a spatula in the mouth of the tube. If this is difficult, filter and return the crystal to the tube. Add 5 ml of water and boil for a minute or two. Cool for 10 minutes, filter, and wash with water; then place on a drying paper disc. The yield is about 80–90 mg; the product melts at 58–59°. It can be crystallized by dissolving in the minimum amount of hot alcohol, filtering, and adding water dropwise until a permanent cloudiness results.

8.2 m-Dinitrobenzene. To 0.5 ml (about 20 drops) of fuming nitric acid in a test tube, add 20 drops of concentrated sulfuric acid. To this mixture add 300 mg (10 drops) of nitrobenzene. Place the tube in a beaker of water that has just been heated to boiling and allow to stand for 10–15 minutes with frequent shaking. Cool and add cautiously 5 ml of water; stopper and shake the tube vigorously. Cool and filter off the crystals; then wash them repeatedly with 1–2 ml of water. Drain the crystals and transfer them to a test tube. Add 3 ml of methanol, heat to boiling, filter, add a few drops of water to the filtrate, and cool. The crystals that separate out are filtered and dried in air. The yield is about 250 mg; the crystals melt at 89–90°.

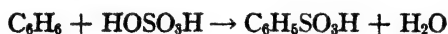
Note: For the preparation of 2,4-dinitrotoluene from toluene and other examples of nitration, see pages 313–315.

Sulfonation. Sulfonation is not extensively employed because the sulfonic acids as a rule are soluble. Occasionally, however, in the identifi-

cation of aromatic ethers, halides and hydrocarbons the compound is first chlorosulfonated to yield the sulfonyl chloride which is then converted to the sulfonamide. Sulfonation, however, is an important reaction of aromatic compounds.

One of the most common methods of distinguishing between aromatic and aliphatic hydrocarbons is to note the difference in the rates of their reactions with sulfuric acid. Aromatic hydrocarbons readily form sulfonic acids when heated with concentrated sulfuric acid at temperatures varying from 80° to 200°. Saturated paraffin hydrocarbons, on the other hand, do not react with sulfuric acid under comparable conditions.

The general method for the preparation of a monosulfonic acid is to heat the aromatic compound with excess of concentrated sulfuric acid at temperatures varying from 80–200° or even higher. The end of the reaction is indicated by complete solubility of a small sample when diluted with water. During sulfonation water is formed, and consequently there is a dilution of the sulfonating medium:

$$C_6H_6 + HOSO_3H \rightarrow C_6H_5SO_3H + H_2O$$

For this reason an excess of 30–40 per cent or more over the calculated amount of sulfuric acid is used. An increase in the rate of sulfonation may be obtained by the addition of sulfur trioxide to the sulfuric acid. Ordinary concentrated sulfuric acid contains about 96–98 per cent of H_2SO_4, the rest of the liquid being water. It is possible to add sufficient sulfur trioxide to convert this water to sulfuric acid and thus produce 100 per cent acid. Addition of still more sulfur trioxide to 100 per cent sulfuric acid gives a sulfonating mixture known as fuming sulfuric acid, or oleum. For laboratory preparations fuming acid containing 5–25 per cent of sulfur trioxide is employed. In general, fuming acid is used for the introduction of the second and third sulfonic acid groups and for the sulfonation of compounds containing nitro groups and other substituents that inhibit sulfonation. The presence of hydroxyl and amino groups is of benefit in sulfonation. For example, phenol may be sulfonated with greater ease than benzene, whereas nitrobenzene requires fuming sulfuric acid. Another sulfonating agent is chlorosulfonic acid. Chlorosulfonic acid is used in special cases because it sulfonates at a particular position. For example, with sulfuric acid toluene yields for the most part *p*-sulfonic acid, whereas with chlorosulfonic acid it forms chiefly *o*-sulfonic acid. The reaction with chlorosulfonic acid may proceed further with the formation of acid chloride. This reaction is useful in the preparation of derivatives for the identification of ethers, halides, and hydrocarbons, since the resulting chloride is readily converted to the sulfonamide by

ammonolysis, thus eliminating the isolation of the sulfonic acid salt and conversion of the latter to the sulfonyl chloride. The reaction of the aromatic compound with chlorosulfonic acid to give the sulfonyl chloride is termed *chlorosulfonation.* In the sulfonation of polynuclear compounds, it becomes necessary to use catalysts to accelerate the reaction; among the catalysts used are iodine, mercury, and vanadium salts.

Sulfonic acids are usually separated by means of their sodium, calcium, or barium salts. The reaction mixture is poured into water. The alkali salt in many cases is separated by the addition of sodium chloride, potassium chloride, sodium acetate, ammonium chloride or other salts. A more general method is to neutralize the diluted mixture with calcium, barium, or lead carbonate and filter the insoluble sulfate from the desired sulfonate. The filtrate, which contains the salt of the sulfonic acid, is concentrated by evaporation to the point of crystallization. The sodium salt is obtained by boiling one of the other salts with a solution of sodium carbonate. The precipitated carbonate of calcium or barium is filtered off and the filtrate is evaporated to obtain the sodium sulfonate. Aminosulfonic acids, having both a proton-repelling and a proton-accepting group, form some type of internal salt and hence their solubility in water is not great. A number of aminosulfonic acids may be separated either directly from the cold reaction mixture or, after diluting with water, by filtering off the precipitated aminosulfonic acid. Since filtration of concentrated sulfuric acid is difficult, dilution with water is the more convenient method. The following procedures illustrate the preparation of an aminosulfonic acid, of the sodium salt of a sulfonic acid, and of a sulfonyl chloride.

8.3 Sulfanilic acid. Place in an 8-inch tube immersed in a beaker of cold water 1.5 ml of concentrated sulfuric and 1 ml of fuming sulfuric acid (15–20 per cent SO_3). Add dropwise 0.5 ml of aniline. The solid that separates is aniline sulfate. Provide the tube with a cork through which is fitted a piece of glass tubing 6–8 mm in diameter and 20–25 cm in length. Heat the mixture in an oil bath at 180° for about 1 hour. Cool to room temperature and add the contents very slowly to 20 ml of water. Cool to 5–10° and filter off the crystals. Wash twice with 2 ml of water. To purify the crude acid suspend in 10 ml of water, heat to 80°, and then add dropwise, with stirring, dilute sodium hydroxide solution until solution is complete. Add 100 mg of charcoal and a pinch of Filter-cel and filter with suction. Add to the filtrate some dilute hydrochloric acid, with stirring, until the mixture is distinctly acid to the indicator. Cool, filter the crystals with suction, wash once with distilled water, and dry on a paper disc. The yield is about 500 mg.

8.4 Sodium benzenesulfonate. Place in an 8-inch tube 5 ml of fuming sulfuric acid that contains 6–8 per cent sulfur trioxide. Clamp the tube securely on a stand so that it rests inside an empty 250-ml beaker. Wear goggles. Place a thermometer in the tube and, by means of a dropper, add 1 ml of benzene over a period of about 5 minutes, in portions of 3–4 drops at a time. As each portion is added, stir the acid cautiously with a thermometer until the benzene layer goes into solution. Keep the temperature of the reaction mixture at 35–50° by adding water to the beaker if the temperature rises above 50°. When all the benzene has been added and dissolved completely, pour the acid mixture very slowly and cautiously, with stirring, into a beaker containing a solution of 4 g of common salt in 20 ml of water. Add, in small portions, 1 g of solid sodium carbonate to neutralize part of the acid. Place the beaker in an ice-salt mixture and allow to stand for 30 minutes, with occasional stirring. If crystallization does not begin immediately on cooling, scratch the walls of the beaker lightly with the stirring rod. Filter by suction and press the crystals to remove the mother liquor as completely as possible. Wash with 2–3 ml of cold saturated salt solution, then with 2–3 ml of alcohol. Drain well and dry on a filter paper or porous plate. If a pure product is desired, recrystallize from ethanol. For the preparation of benzene-sulfonyl chloride the crude salt is satisfactory. For this purpose the salt is dried in the oven at 105–110°. The yield is about 1.5–2 g.

8.5 p-Acetaminobenzenesulfonyl chloride. Place 1 g of dry acetanilide in an 8-inch distilling tube. Heat until it melts, and cool for a minute in air and then by rotating in a beaker containing tap water. Arrange the tube as shown in Figure 62, page 178. Use a solid cork in place of the stopper and condenser. Place a beaker containing ice water under the tube so that it is immersed in it. Pour into the tube, all at once, 2.5 ml of chlorosulfonic acid, and replace the stopper.

(**Caution:** Be careful in handling chlorosulfonic acid, as it causes severe burns if it comes in contact with the skin.)

If the reaction does not start at once, lower the ice bath, introduce a rod in the tube, and cautiously break the acetanilide adhering to the tube. Replace the cork and use the cold bath to moderate the reaction if it is too vigorous. When most of the acetanilide has dissolved, place a water bath under the tube and heat at 80–90° for 15 minutes. Cool and pour very slowly, with stirring, into a mixture of 20 g of ice and 20 ml of water. This operation should be performed *in the hood*, and *goggles should be worn.* Rinse the reaction tube with 10 ml of water and unite with the main portion. After 10 minutes filter the mass, breaking

any lumps that may have formed. Wash with three 5-ml portions of water, press the cake to drain the water as much as possible, and use directly for the preparation of the sulfonamide. If the pure sulfonyl chloride or its preparation from the sodium salt of sulfonic acid is desired, proceed in accordance with the directions given in Section 13.15, page 322.

Reduction. The process of reduction consists either in the addition of hydrogen to unsaturated linkages or in the replacement of a more electronegative element, such as oxygen, halogens, and so forth, by hydrogen. From the electron point of view, such replacement involves the removal of oxygen and halogen atoms as ions, and therefore reduction requires that electrons be supplied for the formation of the carbon-hydrogen bond. The electron-donors in such reactions are the reducing agents. A variety of these are used for the reduction of organic compounds, and most of them may be classified in the following categories. (It should be pointed out, however, that this classification is not complete.)

1. *Metals.* Active metals such as sodium are used with alcohol, or, since the reaction of sodium with water is violent, sodium amalgam may be substituted to moderate the reaction. Aluminum and magnesium in amalgamated form are used as specific reducing agents in certain reactions. Zinc is used both in alkaline and in weakly acid and strongly acid media. Amalgamated zinc is reacted with hydrochloric acid in the (Clemmensen) reduction of carbonyl compounds to hydrocarbons. Reduction with tin and iron requires relatively strong acid media.

2. *Ions.* Positive ions that can be oxidized to a higher positive valence, or negative ions that can be oxidized to the free element, are used as reducing agents. Especially useful ones are the following:

$$Fe^{++} \rightarrow Fe^{+++} \qquad S_2O_4^{=} \rightarrow SO_3^{=}$$

$$Sn^{++} \rightarrow Sn^{++++} \qquad SO_3^{=} \rightarrow SO_4^{=}$$

$$S^{=} \rightarrow S^{\circ} \qquad I^{-} \rightarrow I^{\circ}$$

3. *Activated hydrogen.* In catalytic hydrogenation molecular hydrogen is activated to give atomic hydrogen, which then effects the reduction. It should be emphasized that in reductions effected by means of metals or other reducing ions, electrons for the carbon-to-hydrogen bond are supplied by the reducing agent, whereas the hydrogen ions are derived from the medium in which the reaction takes place.

Semimicro catalytic hydrogenation may be accomplished[1] at atmos-

[1] Cheronis and Koeck, *J Chem Educ*, **20,** 488 (1943); Cheronis and Levin, *ibid*, **21,** 603 (1944).

pheric pressure with easily assembled apparatus. The principle of the method consists in bubbling hydrogen gas by means of a ***microporous disperser*** through a solution of the compound to be reduced, in which a small amount (50 mg) of an active catalyst is suspended. The passage of gas in the form of minute bubbles through the solution keeps the catalyst in constant agitation and maintains a high rate of contact between the catalyst and hydrogen. The gas is adsorbed on the surface of the catalyst, undergoes activation, and reacts with the compound. With this method 500 mg of most nitro compounds may be reduced within 10 15 minutes.

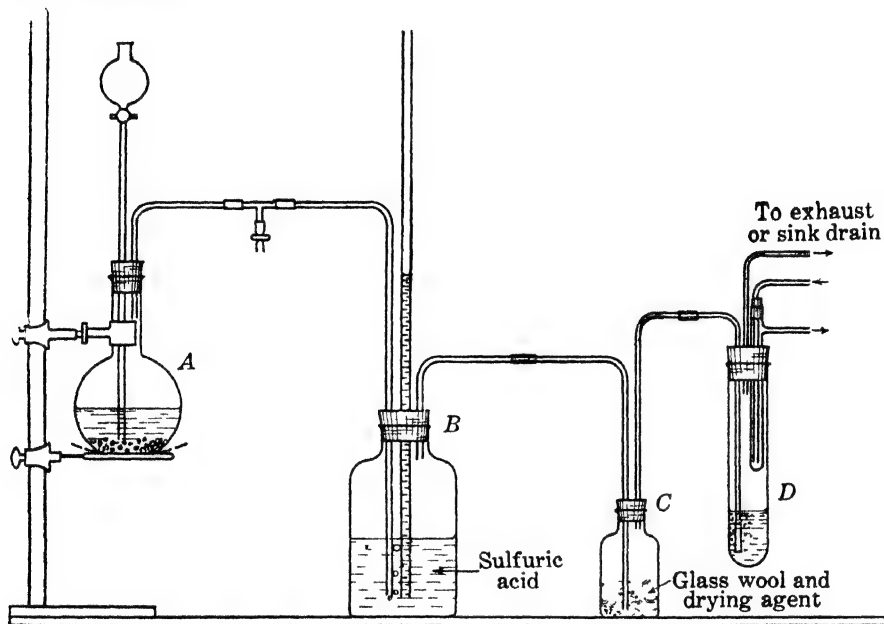



FIGURE 59

Assembly for Semimicro Hydrogenation

Figure 59 shows the apparatus recommended for use in semimicro hydrogenation. The generator (A) is a flask of 500- or 1000-ml capacity. The charge consists of 20 50 g of technical zinc pellets or mossy zinc and 50 ml of water. Dilute (25 per cent) sulfuric acid is added through the separatory funnel. The amount of acid added in the beginning is 10–15 ml. When the flow of hydrogen diminishes so that the bubbles of gas can be counted in the wash bottle (B) at the rate of 1–2 per second, 10 more ml of acid are added. About 10–15 g of zinc and 60–80 ml of dilute sulfuric acid are required for the reduction of 1 gram of most nitro compounds, provided the reaction is complete within 30 minutes.

The hydrogen generator is connected through rubber tubing (preferably red) with a wide-mouthed bottle (B) of 0.5- to 1-liter capacity, containing 250–300 ml of concentrated sulfuric acid. The inlet and outlet and the safety-valve tubes are made of 6-mm tubing; the safety tube is about 1 meter in length. The rise of sulfuric acid above its normal level in the bottle is a measure of the internal pressure of the hydrogen. The height of sulfuric acid should not exceed 30–40 cm, corresponding to about half an atmosphere. During some hydrogenations, particularly when the compound formed is not very soluble in the solvent, the disperser becomes slightly clogged. Another reason for this may be that the greater part of the reaction takes place near the interface of the porous tube and the liquid. In such cases the sulfuric acid in the safety tube begins to rise, and the disperser must be either changed or cleaned through immersion in a test tube containing 5 ml of warm solvent. The solvent is drawn by mild suction a few times into the porous tube until air may be blown easily through the solution. The wash bottle (B) is connected to a 250-ml bottle (C) containing some glass wool and a small layer of calcium chloride. Traces of moisture in the hydrogen do not seem to impede the reaction.

The hydrogenator consists of a regular 8-inch Pyrex tube (D). A greater efficiency is obtained in the agitation of the catalyst if the bottom of the tube is drawn down slightly. The tube is closed by a three-hole rubber stopper through which are attached: (a) the microporous disperser, (b) a microcondenser, (c) an outlet for the excess hydrogen. The microporous disperser is described in detail below. It is connected through a piece of rubber tubing 3–4 mm in diameter and 30–40 cm in length with the bottle (C). The microcondenser is inserted about 80–90 mm into the tube. The outlet is connected with a piece of tubing that leads into the hood or, through a small opening in a window, to the outside. Alternatively the outlet may be connected to a 2-liter bottle filled with water to enable the excess hydrogen to be collected by water displacement. Since the amount of excess hydrogen is not very great, it may be washed down the drain, provided only one hydrogenation is being performed in the laboratory.

The rubber stoppers and rubber tubing should be washed before use, first with soap and water and then with alcohol. It is also advisable to clean the three-hole rubber stopper of the hydrogenator with an abrasive (particularly if it is new and made of black rubber), to remove adhering material. The practice of boiling rubber stoppers with sodium hydroxide in order to remove sulfur, although beneficial, is considered too time-consuming. The use of impure hydrogen and the fact that no difficulty

traceable to rubber tubing and stoppers has been encountered justify the omission of the practice.

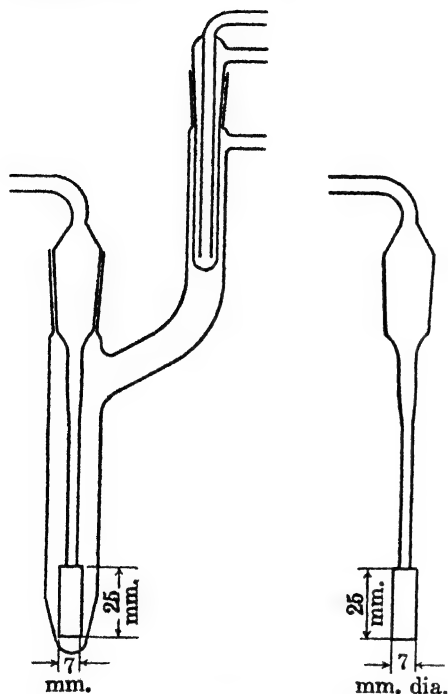



FIGURE 60

Semimicro Hydrogenator with Ground-glass Joints

(Commercial model)

The microporous disperser consists of a glass tube 200–250 mm in length and 4–5 mm in diameter, sealed at one end into a small porous tube. The porous tube is 6 mm in diameter and closed at one end; the length of the porous tube may be varied from 25–35 mm. If small amounts of liquid are to be hydrogenated, the porous tube may be shortened. The glass tube may be sealed to the porous tube by cement or may be directly fused to it. The porous tube or the complete disperser is commercially available at a small price.[2] A complete hydrogenator, with ground glass joints for the disperser and condenser shown diagrammatically in Figure 60, is also commercially available.[2] The best catalysts for semimicro hydrogenation with the apparatus described are platinic oxide and 5 per cent palladium carbon; both of these are commercially available. The palladium carbon is preferred, since different lots have a more uniform activity and it is less expensive. The amount required for most hydrogenations is 50 mg of platinic oxide and 250 mgs of 5 per cent palladium carbon.

8.6 General directions for semimicro hydrogenation. For the hydrogenation of nitro compounds and unsaturated acids, ordinary 95 per cent ethanol is used, although methanol may be an alternative in most cases. In the case of hydroxy compounds, such as allyl alcohol, or unsaturated hydrocarbons, isopropyl ether is used. For 500 mg of substance to be reduced, about 20–25 ml of solvent is sufficient. Approximately 250 mg of 5 per cent palladium carbon or 50 mg of platinic oxide are added to the solvent contained in the hydrogenating tube, and the rubber stopper holding the disperser, microcondenser, and outlet is in-

[2] Wilkens-Anderson Co., Chicago, Ill.

serted. The disperser is connected to bottle (C), Figure 59, and the outlet tube to the exhaust. About 15 ml of 25 per cent sulfuric acid are added to the hydrogen generator, which contains 20–50 g of zinc and 50 ml of water. The gas is allowed to pass through the suspension of palladium carbon for 1–2 minutes to activate it. If platinic oxide is used, the passage of gas will reduce it to platinum black. The displacement of air through the suspension has been found to help rather than hinder the reduction. The time required for conversion of the oxide to platinum black varies from 2–5 minutes; if more than 5 minutes, the activity of the platinic oxide will probably be poor. While the activation of the catalyst is proceeding, the hydrogenating tube is immersed in a 600–800-ml beaker containing water at about 60°. The temperature is kept at 50–60° by adding hot water from time to time. When the catalyst has been activated, the stopper is raised and 500 mg of the substance to be reduced is added. The stopper is replaced and the tube is gently shaken so as to wash down the compound adhering on the sides of the tube. The flow of hydrogen at the beginning of the reaction may be observed in the bubbles emerging in the wash bottle, which can be counted at the rate of 4–6 per second. The flow is reduced after the first 10 minutes to about 3–4 bubbles per second. When the flow of hydrogen diminishes and addition of 5–8 ml of acid is necessary, the rubber tubing that leads from bottle (C) to the disperser is disconnected, the acid is run in rapidly, and the tubing is again connected to the microporous disperser. If a permanent setup is made, it will be convenient to insert a glass stopcock in bottle (C) and connect the stopcock to the exhaust. In this manner the gas pressure may be released without disconnecting the disperser. The time required for the reduction of some of the nitro compounds is 10–20 minutes. If the product is crystalline and melts above 50°, the reaction may be followed by withdrawing 1 ml of its solution through a pipette, placing it in a watch glass and then evaporating. Determination of the melting point provides information as to the extent of reduction. When the reaction is completed, the flow of hydrogen is stopped, the disperser is raised out of the solution, and the tube is allowed to stand for 5–10 minutes to permit settling of the catalyst. The stopper is removed and the liquid poured out slowly so as to retain all the catalyst in the tube. (The catalyst in the tube is used a second and a third time if the same compound is reduced.) The solvent and the reducible compound are put into the tube and the flow of hydrogen is started. When the catalyst is spent, the solution is poured out, water is added, and the suspension poured on a filter. The same paper is used for filtering residues until 10–20 lots have been filtered.

The paper is then incinerated in a clean quartz dish at about 600°. The residues are reworked or sold to the dealers who supply the catalyst.

In most cases the recovery of the product from the solution is accomplished by evaporation of the solvent in a dish over a water bath. This method entails losses, particularly when the product has a considerable vapor pressure at the boiling point of the solvent. The product obtained by the evaporation of the solvent is sufficiently pure in most cases for determination of its melting point. It is usually a little colored by minute amounts of the catalyst and, if the product is to be used further, it must be recrystallized.

Cleaning of the disperser. After the reduction has been completed, the disperser is removed and placed in a 6-inch test tube with a few milliliters of ethanol or methanol. The alcohol is sucked several times into the tube just past the glass junction and then blown out again. It is then removed, and air is blown through to drain it. It is cleaned by immersion in a small amount of aqua regia and heating in the hood until a vigorous reaction begins. It is then allowed to stand for a few minutes and is washed by aspirating water through it. If the suction pump is of metal, the disperser is dipped into 10 per cent sodium hydroxide before aspiration. After washing with water the process is repeated with 2 successive 10-ml portions of alcohol, and the disperser is allowed to dry. If the cement joining the glass to the porous tube cracks or chips, it may be patched with fresh cement.

In some reductions, as in the case of *p*-nitrophenol, there is a tendency for the disperser to clog, owing to the deposition of the product within the pores. Therefore it is advisable to have two dispersers available. After the disperser has been changed, the clogged tube is freed by aspirating warm alcohol through it. The procedures given below illustrate a number of reductions useful in the preparation of derivatives.

8.7 Aniline (*Use of tin as a reducing agent*). Place 2 ml of nitrobenzene and 9 ml of concentrated hydrochloric acid in an 8-inch tube and arrange for reflux with a microcondenser. Add in small portions 4.5 g of granulated tin. The reaction is controlled by the rate of addition of the metal. Shake the tube from time to time. When all the tin has been added, boil gently for 20 minutes until the odor of nitrobenzene disappears. Cool and add 4.5 g of solid sodium hydroxide in small portions, cooling the tube by immersion in cold water. Stir with a rod. When all the alkali has dissolved, steam-distil by using the setup shown in Figure 27, page 50, and utilizing, as a boiling tube, the 8-inch tube containing the reaction mixture. The volume of the reaction mixture may be divided into 2 portions and each distilled until 5 ml of distillate

have been collected. Add 2 g of sodium chloride to the combined distillates (10 ml) and shake until the salt is dissolved.

Extract with three 4-ml portions of ether and unite the ethereal solutions. Add 2 g of sodium hydroxide (flake or crushed pellets) and shake. If an aqueous solution forms, pour the ether into a dry tube and add 2 g of fresh sodium hydroxide. Allow to stand overnight. Pour the ether into a large distilling tube, add two small boiling stones, and distil the ether from a water bath. Remove the water bath and empty the ether from the receiving tube into the bottle designated for this purpose; wipe the distilling tube with a cloth and heat it with a small smoky flame. When the temperature reaches 175°, change the receiving tube. The fraction that boils at 180–185° is collected in a tared tube. The yield is about 1 g.

8.8 β-Phenylhydroxylamine (*Use of zinc in slightly acid solution*). Place in an 8-inch tube 1 ml of nitrobenzene, 20 ml of water, and 0.6 g of ammonium chloride. Add in small portions 1.6 g of zinc dust, shaking the contents of the tube. The reduction of nitrobenzene to β-phenylhydroxylamine proceeds rapidly and with evolution of heat, the temperature rising to 50–60°. When all the zinc dust has been added, shake the tube for a few minutes longer, filter off the zinc oxide, and wash with 2–3 ml of hot water. Add to the filtrates 6 g of common salt. Shake and cool. Long yellow needles of β-phenylhydroxylamine separate. Filter the crystals, wash with cold water, and dry in a vacuum desiccator.

8.9 Hydrazobenzene (*Use of zinc in alkaline solution*). Place in an 8-inch tube arranged for reflux 1 g of nitrobenzene, 1.5 ml of 6 *N* sodium hydroxide, and 6 ml of ethanol. Heat the mixture in a water bath to about 75°. Remove the burner and add zinc dust in 0.2 g portions until about 1.5 g have been added and the solution becomes pale yellow. The zinc dust is added by raising the cork slightly for a moment. The reaction is allowed to subside before any further amount of zinc dust is added. If it becomes violent, remove the hot bath and cool the tube. When the reduction is complete, the mixture is poured into 20 ml of water and cooled; then 5–6 ml of concentrated hydrochloric acid are added slowly, with stirring, until the solution is definitely acid. The crystals of hydrazobenzene that separate are filtered and washed with cold water.

Note: In the following preparations (8.10–8.15), use is made of catalytic hydrogenation as described in Section 8.6 for the reduction of: (a) aldehydes to alcohols; (b) olefinic linkages; (c) nitro compounds to amino compounds. The latter type of reduction is the most useful for identification work.

8.10 Reduction of piperonal. Place 200 mg of 5 per cent palladium carbon[3] in the hydrogenating tube and add 25 ml of ethanol. Pass hydrogen for 2 minutes and then add 500 mg of piperonal. Heat the bath to 60° and pass hydrogen for 15 minutes. Filter and wash residue with two 5-ml portions of alcohol. Evaporate the filtrates in a dish over a water bath until a small amount of solvent remains, then conduct the evaporation slowly. Cool the residual oil by placing the dish in a freezing mixture. Scratch the oil with the spatula to make it solidify. Scrape the crude mass and transfer it into a tube. Add 12–15 ml of heptane or petroleum ether, boil to effect solution, and filter by suction into an 8-inch test tube having a side arm. Extract the oily mass remaining in the solution tube, which is crude piperonyl alcohol, using the filtrates from the first crystallization. Cool the filtered solution and scratch the inner surface of the tube with a glass rod. Allow to stand 10 minutes and filter. Conduct successive extractions of the crude piperonyl alcohol, using the filtrates from the previous crystallization, until the crude residue is exhausted. Collect the crystals on the suction funnel and wash with a few milliliters of the pure solvent. Place the crystals on a drying disc. The yield is about 400 mg of crystals that melt at 52–53°.

Note: Salicylaldehyde is reduced to salicyl alcohol by the same method. Hydrogen is passed for 25–30 minutes. The yield from 500 mg of salicylaldehyde is 350–400 mg of crystals that melt at 86°.

8.11 Reduction of maleic acid. Use standard method described in Section 8.6. Toward the end of the reaction there is a tendency for the catalyst to flocculate and settle out. The reduction is nearly complete in 20 minutes. The melting point of the product is usually about 172–175°. In order to raise the melting point of the crystals to 180°, it is necessary to continue the reduction for about 15–20 minutes longer with frequent shaking of the tube. An alternative method is to discontinue the reduction at 20 minutes and recrystallize the product. The use of palladium carbon gives better results than platinic oxide.

Note: In the following preparations (8.12–8.15) 500 mg of the substance to be reduced are used in each case.

8.12 Reduction of p-nitrophenol. The standard method described in Section 8.6 is used; the solvent is 25 ml of ethanol. Clogging of the microporous disperser after reduction has passed the midpoint necessitates cleaning of the disperser. The clogged disperser is cleaned with

[3] Baker and Co., Phillipsburg, N. J.; Wilkens-Anderson Co., Chicago, Ill.

alcohol as described; a different disperser is inserted if cleaning is not sufficient. After the reduction is complete, the alcohol is poured into a small dish and evaporated to a volume of 6–8 ml. About 2 ml of water are added, the solution is cooled, and the crystals of *p*-aminophenol are filtered. *o*-Nitrophenol is reduced in the same manner.

8.13 p-Nitrotoluene. The standard method is used. After the reduction is complete and the alcoholic solution has been poured into a dish, dilute hydrochloric acid is added drop by drop until the solution is acid to litmus. The solution is evaporated until all the alcohol has been driven out; then about 5 ml of water are added and the contents of the dish are cooled for a few minutes and filtered. Dilute sodium hydroxide is added to the filtrate by means of a dropper until the solution is distinctly alkaline. The oil that separates out soon solidifies. The mixture is cooled and the crystals of *p*-toluidine are filtered.

8.14 Nitrobenzene. The standard method is used. The alcohol is poured into a dish and neutralized with glacial acetic acid. After the alcohol has been evaporated, a mixture of 4 ml of acetic anhydride and 2 ml of glacial acetic acid is added to the residue. The mixture is boiled gently over a small direct flame for about 3 minutes. Water (15 ml) is added, and then 6 *N* sodium hydroxide solution, until the reaction is neutral or only slightly acid. After cooling, the crystals of acetanilide are filtered off. No further purification is required.

8.15 m-Dinitrobenzene. The standard method is used. The reduction is complete when the yellow color of the solution disappears. The alcoholic solution is poured into a dish, neutralized with dilute hydrochloric acid, and then evaporated to dryness. The salt is converted into the diamine by suspending it in 5 ml of benzene and adding ammonium hydroxide solution dropwise until, on shaking, the odor of ammonia is detected. The benzene layer is separated and evaporated.

Oxidation. The term oxidation as applied to organic compounds has a restricted meaning. In general, any removal of hydrogen atoms that leads to the formation of an unsaturated linkage, any rupture of a carbon-to-carbon bond, and any replacement of one or more hydrogen atoms may be regarded as oxidation reactions, since all involve electron shifts from the carbon atom. Thus the replacement of a hydrogen atom in a hydrocarbon by chlorine could be regarded as oxidation. The term, however, as used in a restricted sense applies to: (a) reactions involving dehydrogenation; (b) reactions involving the introduction of oxygen or a group containing oxygen—this includes such reactions as the hydration of olefins, rupture of carbon-to-carbon linkages with the formation of aldehydes, acids, and so on.

Most oxidizing agents contain ions that are capable of accepting electrons and of being thereby reduced. The following is a partial list of the more common oxidizing agents used in organic reactions.

1. *Oxygen.* Molecular oxygen is not easily activated at room temperatures. A few aldehydes may be oxidized slowly by air. At higher temperatures in the presence of copper, vanadium oxide and other catalysts air is used extensively for vapor-phase oxidations. Ozone may be used in the oxidation of unsaturated linkages, through the formation of ozonides, followed by decomposition to carbonyl or carboxyl compounds.

2. *Peroxides.* Hydrogen peroxide may be used in alkaline media (Dakin's reaction) for the oxidation of *o*-hydroxy aldehydes to the dihydroxy derivatives; with acetic acid hydrogen peroxide oxidizes olefinic linkages to the dihydroxy (glycol) stage. Lead dioxide is used for the oxidation of triphenylmethane and related hydrocarbons to the alcohol stage.

3. *Compounds of chromium, manganese, and iron.* Sodium and potassium dichromate, chromic oxide, manganese dioxide, potassium permanganate, ferric chloride, and ferric ammonium sulfate are among the more common oxidizing agents used in the laboratory. The dichromates are strong oxidizing agents used in acid solutions, nearly always with sulfuric acid; they are particularly efficient in the oxidation of alcohols to aldehydes and acids, of phenols to quinones, and of aromatic side chains. Chromium trioxide mixed with acetic acid, or a mixture of acetic acid, acetic anhydride, and sulfuric acid, is used for the oxidation of aromatic hydrocarbons to aldehydes or quinones. Potassium permanganate in neutral or alkaline solution is used for the oxidation of side chains of cyclic compounds. Ferric salts are suitable for the oxidation of phenols to quinones, hydroxylamines to nitroso compounds, and other mild oxidations.

4. *Peracids and their salts.* Periodic acid, persulfuric acid (Caro's acid, $H_2S_2O_8$), potassium persulfate, perphthalic acid, and others, are used for the oxidation of specific linkages. Periodic acid is used to oxidize glycols and other polyhydroxy compounds resulting in cleavage to carbonyl compounds. The persulfates are used for the oxidation of aromatic primary amines to nitroso compounds. Perphthalic acid serves to oxidize unsaturated linkages to oxides.

5. *Hypohalites.* Sodium hypochlorite and solutions of bromine and iodine in alkali are used as oxidizing agents in the haloform reaction and in conversion of amides to amines by decarboxylation (Hofmann reaction).

6. *Nitric acid.* Concentrated nitric acid is a strong oxidizing agent

used only in cases that preclude nitration. It oxidizes cyclohexane to adipic acid, nicotine to nicotinic acid, and benzoin to benzil.

7. *Other oxidizing agents.* Among other oxidizing agents, the following may be mentioned; potassium ferricyanide, used as a mild oxidizing agent; lead tetraacetate, a strong oxidizing agent used for oxidations similar to those effected with periodic acid; the oxides of copper, silver, and mercury, which are mild oxidizing agents.

8.16 Oxidation of lower alcohols to aldehydes and ketones. The apparatus is shown diagrammatically in Figure 61. An 8-inch distilling tube is connected to the regular condenser-receiver setup and provided with a one-hole rubber stopper. Through the opening of the rubber stopper, a pipette dropper (graduated, if possible) is fitted.

FIGURE 61
Semimicro Apparatus for Oxidation of Alcohols

Dissolve 2 g of sodium dichromate into 8 ml of water and then add slowly 3 ml of concentrated sulfuric acid. Place the mixture in the distilling tube and add 2 small boiling stones. Draw 1 ml of the alcohol to be oxidized into the pipette dropper and fit the latter carefully into the opening of the rubber stopper. Insert the rubber stopper into the mouth of the distilling tube and heat the latter by means of a small flame until the dichromate solution just begins to boil. Remove the flame and allow the mixture to cool for 1 minute. Add the alcohol at the rate of 1 drop every 2 seconds and rock the tube gently so as to mix the contents. After 5 drops have been added, heat the tube with a small flame so that distillation begins, and then continue supplying the alcohol until all has been added; remove the flame if at any time boiling and distillation become too rapid. When all the alcohol has been added, heat the tube until 6 ml of distillate have been collected.

Formaldehyde and acetaldehyde cannot be separated by fractionation; acetone, butanone, propanal, and other lower aldehydes boiling below

100° can be separated by fractionation. For the preparation of derivatives it is not necessary to separate the pure compound, but instead a fraction boiling 5° above and below the boiling point of the carbonyl compound may be collected. For example, in the oxidation of 2-propanol, the fraction boiling at 50–60° is collected and used directly for the preparation of the derivative of acetone. Similarly in the oxidation of 2-butanol, the fraction boiling at 75–85° is collected.

Oxidation of aldehydes to acids. The aldehyde is treated with alkaline permanganate. If the acid is insoluble in water, the mixture is acidified and the acid filtered; if the acid is soluble in water, the reaction mixture is evaporated to half of its original volume, cooled, acidified, and the acid extracted with ether.

8.17 m-Nitrobenzoic acid. Place 500 mg of *m*-nitrobenzaldehyde, 5 ml of water, and 6 drops of 6 *N* sodium hydroxide solution in a 125-ml Erlenmeyer flask. Place in another 125-ml flask 1 g of potassium permanganate with 25 ml of water and heat nearly to boiling. Add the permanganate solution to the mixture in small (5-ml) portions, shaking the flask constantly by hand. When about 20 ml of permanganate solution have been added, shake well and wash the sides of the flask with a small amount of water. Allow the mixture to stand for 2 minutes, heat nearly to boiling, and test for excess of permanganate by dipping a rod into the flask and transferring a drop of the liquid into a test tube containing 10 ml of water. If the purple color of the permanganate does not disappear, oxidation is complete; otherwise more permanganate is added to the flask until the color persists. Filter the solution from the manganese dioxide, and change the filter paper after about 10 ml of solution have been filtered to facilitate rapid filtration. Return the colored solution to the flask; add 2 ml of dilute sulfuric acid and about 500 mg of sodium bisulfite. If the solution does not decolorize, add a small amount of solid bisulfite until the permanganate and adhering film of manganese dioxide have been changed to the manganous state. Cool and filter off the crystals of *m*-nitrobenzoic acid; wash with water and recrystallize from 4 ml of methanol. After the hot alcoholic solution of the acid has been filtered, add water dropwise until a permanent cloudiness results. Cool and filter. The yield is 450–500 mg. The filtration of manganese dioxide may be omitted and an excess of bisulfite added to convert all the manganese dioxide to the manganous salt. It has been found, however, that the purity of the product is higher if the manganese dioxide is removed by filtration.

8.18 n-Butyric acid. Place in a 125-ml Erlenmeyer flask 3 ml of 6 *N* sodium hydroxide solution and 15 ml of 3 per cent hydrogen peroxide

solution. Heat to 60° and add 500 mg of butanal. Shake the flask at intervals and keep at 60–70° for 10 minutes. If the odor of aldehyde persists, add 5 or more ml of hydrogen peroxide and heat for 5–10 minutes longer. Add dilute sulfuric acid slowly until the *p*H of the solution is 8–9 (use either universal indicator or phenolphthalein). Evaporate to dryness and convert the salt to *p*-toluidide by using Procedure 9.1, page 208. If the acid is a solid and insoluble in water, the solution is acidified at the end of the oxidation, and cooled; the crystals are then filtered.

Oxidation of side chains. Acid dichromate, or alkaline permanganate solution, may be used for the oxidation of the side chains of aromatic hydrocarbons to the carboxylic stage. Generally, permanganate oxidation is preferred for the more resistant side chains—that is, in the presence of nitro groups, or whenever extensive degradation by oxidation is necessary.

8.19 p-Chlorobenzoic acid. Place 1.5 g of solid potassium permanganate, 25 ml of water, and 0.5 ml (5–8 drops) of 6 *N* sodium hydroxide and 2 boiling stones in an 8-inch tube arranged for heating under reflux. Lastly, add 400–500 mg of *p*-chlorotoluene and boil gently for 1 hour or longer until the purple color of the permanganate has disappeared. Cool the reaction mixture and carefully acidify with dilute sulfuric acid; then heat to boiling. If there is an appreciable amount of manganese dioxide present, add a small amount of solid sodium bisulfite. Cool and filter the acid; recrystallize from 4–5 ml of hot alcohol. Filter the hot alcoholic solution and add water dropwise until a permanent cloudiness results. Cool, and filter off the crystals. The yield is 300–400 mg.

Note: *o*-, *m*-, and *p*-nitrotoluene are oxidized to the respective nitrobenzoic acids by the same method. Similarly, *o*-, *m*-, and *p*-xylene are oxidized, respectively, to phthalic, isophthalic, and terephthalic acids. In the latter, since there are 2 side chains to be oxidized, the amount of all reagents except the hydrocarbon is doubled. A 125-ml Erlenmeyer flask is used for the boiling vessel, and the mixture is heated for 1.5–2 hours.

8.20 p-Nitrobenzoic acid. In an 8-inch tube dissolve 1 g of sodium dichromate in 3 ml of water and add 2 ml of concentrated sulfuric acid. Add 200–250 mg of *p*-nitrotoluene and 2 boiling stones. Boil for 20–30 minutes. Cool and add 2–3 ml of water; then filter. Wash three times with water. Recrystallize from 4–5 ml of hot methanol. Filter the hot methanol solution and add water to the filtrate until a permanent cloudiness results. Cool, and filter off the crystals. The yield is 180–230 mg.

Oxidation of phenols and hydrocarbons to quinones: *8.21 p-Benzoquinone.* Arrange for steam distillation as shown in Figure 27. Place

in the 8-inch tube 3 ml of water, 0.5 ml of concentrated sulfuric acid, and 500 mg of hydroquinone. Connect all the apparatus, using as a receiver an 8-inch tube immersed in ice water. Raise the cork of the tube containing the hydroquinone and add 0.7 g of solid manganese dioxide. Pass steam until 6–8 ml of distillate has been distilled. Filter the cooled distillate with suction, wash with cold water, press, and dry. Store the crystals in a dark bottle. The yield is about 350–400 mg.

8.22 β-Naphthoquinone. Using a small beaker, dissolve 500 mg of 1-amino-2-naphthol hydrochloride in 5 ml of water, and heat to 30°. Filter the solution in an 8-inch tube and add all at once, with shaking, a freshly prepared solution of 3 g of ferric ammonium alum, $Fe_2(SO_4)_3 \cdot (NH_4)_2SO_4 \cdot 24H_2O$, in 12 ml of water and 0.5 ml of hydrochloric acid. If ferric ammonium alum is not available, use 0.8 g of ferric chloride ($FeCl_3 \cdot 6H_2O$) dissolved in 4 ml of water and 0.5 ml of concentrated hydrochloric acid. In either case, prepare the solution of the ferric salt by heating until it dissolves, filtering the solution into a flask, and cooling to about 30°. The β-naphthoquinone separates within a few minutes after the addition of the oxidizing solution. Filter by suction and wash several times with water. Drain the crystals and place on paper to dry. The yield is about 300–350 mg.

8.23 Anthraquinone. Place 1 g of chromic oxide in an 8-inch test tube arranged for reflux. Weigh this material rapidly and carefully. Add 2 ml of water, heat for a minute, and then add 6 ml of glacial acetic acid. Heat until the oxide has dissolved. Cool to 50° and add, in small portions, 500 mg of anthracene. Mix the solution well after each addition. When all the anthracene has been added, throw in a boiling stone and boil gently for 10–15 minutes. Allow to cool; then transfer the contents of the tube to a small beaker containing 25 ml of water. Cool and filter off the crystals.

Halogenation: a. *Chlorination of hydrocarbons.* Few derivatives are prepared by the introduction of chlorine into organic compounds. Even though recently methods have been developed for rapid laboratory chlorination, this process is seldom used.[4] The method proposed by Cutter and Brown[5] is particularly suitable for semimicro work since it uses sulfuryl chloride and avoids gaseous chlorine. It may prove effective in the identification of some aliphatic cyclic hydrocarbons. It is possible to fractionate the mixture of halides produced so as to separate a pure alkyl or cycloalkyl halide, which may be subsequently converted to an anilide, *p*-toluidide, or *S*-alkylisothiourea picrate (page 281).

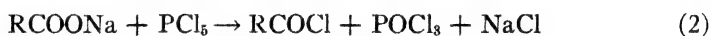
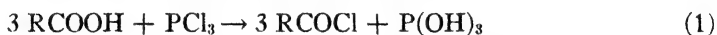
[4] Cheronis, *J. Chem. Educ.*, **20**, 611 (1943).
[5] Cutter and Brown, *ibid.*, **21**, 443 (1944).

b. *Replacement of hydroxyl by chlorine.* The replacement of the hydroxyl radical of alcohols with chlorine is accomplished by the use of hydrochloric acid and zinc chloride, phosphorus chlorides, and in some cases by thionyl chloride. Of greater importance for the preparation of derivatives is the replacement of the hydroxyl group in a carboxylic acid, with the production of acid chlorides. *p*-Nitrobenzoyl chloride and 3, 5-dinitrobenzoyl chloride are important reagents for the identification of alcohols; further, the *p*-toluidides, anilides, and other derivatives for the carboxylic acids may be prepared by converting the acid to acyl or aroyl chloride and reacting the latter with an amine.

The chlorides are usually prepared by the action of phosphorus trichloride, phosphorus pentachloride, or thionyl chloride on the acids:

$$3\ RCOOH + PCl_3 \rightarrow 3\ RCOCl + P(OH)_3 \qquad (1)$$

$$RCOONa + PCl_5 \rightarrow RCOCl + POCl_3 + NaCl \qquad (2)$$

$$RCOOH + SOCl_2 \rightarrow RCOCl + HCl + SO_2 \qquad (3)$$

The particular method to be used is determined by the practicability of the separation of the chloride from the by-products of the reaction and from the excess of the reagent used. Thus, in the laboratory, phosphorus trichloride is used for the lower fatty acids because their chlorides are more volatile than phosphorus acid. The acid, together with 1.5 times the amount of phosphorus trichloride, as indicated in equation (1), is refluxed, and then the acid chloride is distilled from the viscous phosphorus acid and fractionated. Phosphorus pentachloride is reacted with aromatic acids as shown in Equation (2). The dry, finely pulverized potassium or sodium salt of the acid is mixed with a little more than the calculated amount of the pentachloride and heated until the reaction is finished. The resulting oxychloride ($POCl_3$) is removed by distillation. If the boiling points of aroyl chloride and phosphorus oxychloride are too close, then the mixture is added to finely chopped ice. The oxychloride decomposes instantly, whereas the aroyl chloride does not react appreciably at this temperature. The aroyl chloride is either separated by filtration or extracted with ether, dried, and then fractionated.

The use of thionyl chloride has the great advantage of forming gaseous products—sulfur dioxide and hydrogen chloride—as shown in Equation (3), thus rendering the purification simpler. Moreover, it permits the preparation of small amounts of halide for the purpose of identification. For most cases, a little more than the theoretical amount of thionyl chloride is added to the acid and warmed at 60–70° for an hour. If the acid chloride boils above 100°C., it is necessary to heat only to this temperature to remove the excess of thionyl chloride. The use of the crude

halide for the preparation of anilides and *p*-toluidides is illustrated in the experimental procedures described on pages 210 to 212.

8.24 3,5-Dinitrobenzoyl chloride. Arrange an 8-inch distilling tube as shown in Figure 62. The side-arm of the distilling tube is connected with a receiving tube partially filled with water; the short delivery-tube reaches just above the water level. (**Caution:** Use the hood and wear goggles throughout.) Remove the stopper and introduce into the tube 1 g of 3,5-dinitrobenzoic acid and 1.3 g of phosphorus pentachloride. Replace the stopper and heat the tube with a microburner until a vigorous reaction begins; remove the flame momentarily until the reaction subsides and then adjust it so that slow refluxing takes place. Heat for 15 minutes. Remove the flame and insert a thermometer in place of the condenser; also insert a dry receiving tube. Heat the tube (moving the flame up and down) until all the oxychloride has distilled and the thermometer indicates a temperature of 120°. Remove flame and add 5 ml of *dry* carbon tetrachloride. Cool in an ice salt bath for 5 minutes; then filter the crystals with suction and wash them with 1 ml of solvent. Return the filtrates to the distilling tube and distill until 2 ml of solution remain. Disconnect and cool the distilling tube as before. Remove the mass of crystals by means of a rod directly to a drying disc or microplate and dry in air for about ten minutes. The second crop of crystals (350–400 mg) is pure, melting at 74°; the first crop (600–700 mg) melts at 67–69°; upon crystallization from 2 ml of solvent the yield is about 400 mg, melting at 72–73°. Both lots may be used for the preparation of 3,5-dinitrobenzoates (pages 221–226). The acid chloride should be stored in a dry tube or small bottle and the stopper sealed with wax.

FIGURE 62
Apparatus for Preparation of Acid Halides

c. *Bromination.* Substitution of hydrogen by bromine takes place in most cases readily and is easily controlled, since the amount of bromine and the rate of addition may be regulated. For the bromination of hydrocarbons, aliphatic carboxylic acids, and aromatic compounds that have meta-directing groups, catalysts are usually required; among the

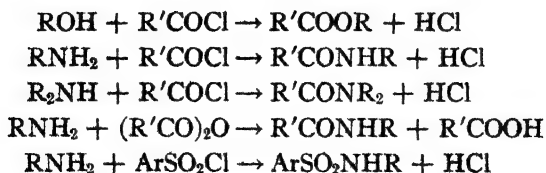
most commonly used catalysts are iron or iron salts, phosphorus or phosphorus halides, sulfur or its halides, and iodine. For the bromination of aromatic compounds having *ortho-* and *para-*directing groups, bromination takes place rapidly without the acid of catalysts. Phenols brominate rapidly in the presence of water. This reaction is used in the preparation of derivatives for the identification of phenol (page 220). Bromination is also accomplished by addition of bromine to the solution or suspension of the compound in glacial acetic acid.

Bromination in the presence of water is accomplished by the addition of an aqueous solution containing potassium bromide and bromine as illustrated in Experiment 8.26.

8.25 2, 4, 6-Tribromoaniline. Place 2 ml of glacial acetic acid in a 6-inch test tube. Add *carefully* about 0.5 ml of bromine by means of a graduated dropper. Add, dropwise, 0.3 ml of aniline and allow the mixture to stand for 5 minutes. Add 2 ml of water and cool for 5 minutes. Filter the crystals and wash with 2 ml of 50 per cent methanol. Transfer the crystals to an 8-inch tube, add 4 ml of methanol, and heat nearly to boiling, adding more methanol until the solid has dissolved completely. Filter and add water dropwise to the hot solution until a cloudiness results. Cool and filter the crystals. The yield is 500–600 mg of crystals which melt at 119°.

8.26 Tribromophenol. Place in an 8-inch tube 0.8 g of potassium bromide and add 5 ml of water. Shake the tube until the salt dissolves; add *carefully* 0.5 g of bromine. Place in a 6-inch test tube 100 mg of phenol, 1 ml of methanol, and 1 ml of water. Add about 1.5 ml of the prepared bromine solution and shake the tube; continue the addition of bromine solution until the mixture retains a yellow color after shaking. Add 3–4 ml of water and shake vigorously. Filter the bromophenol and wash well with water. Dissolve the crystals in hot methanol and filter; add water dropwise to the methanol solution until a permanent cloudiness results. The yield is 180–200 mg of crystals which melt at 95°.

Acylation. Hydroxy compounds (ROH), primary amines (RNH_2), and secondary amines (R_2NH) react with acid chlorides and anhydrides, the reactive amino hydrogen and hydroxyl hydrogen being replaced by the acyl group:

$$ROH + R'COCl \rightarrow R'COOR + HCl$$
$$RNH_2 + R'COCl \rightarrow R'CONHR + HCl$$
$$R_2NH + R'COCl \rightarrow R'CONR_2 + HCl$$
$$RNH_2 + (R'CO)_2O \rightarrow R'CONHR + R'COOH$$
$$RNH_2 + ArSO_2Cl \rightarrow ArSO_2NHR + HCl$$

It should be noted that the hydroxy compounds yield esters and the amines yield substituted amides, which are among the most important derivatives for the identification of hydroxy compounds and primary and secondary amines. Among the most commonly used reagents for the introduction of acyl (RCO-) aroyl (ArCO-), and arylsulfonyl ($ArSO_2$-) groups are: acetic anhydride, acetyl chloride, benzoyl chloride, *p*-nitrobenzoyl chloride, 3,5-dinitrobenzoyl chloride, benzenesulfonyl chloride, and *p*-toluenesulfonyl chloride.

For acetylation, the usual procedure is to heat the amine or hydroxy compound with acetic anhydride; addition of a small amount of acetic acid or trace of sulfuric acid to the mixture sometimes increases the rate of acetylation. As discussed in greater detail on page 254, diacetyl derivatives, $RN(COCH_3)_2$, are likely to form with some primary amines. Acetylation by means of acetyl chloride, although feasible, is not advisable except in special cases because acetyl chloride is more difficult to keep and handle than acetic anhydride. In difficult acetylations pyridine may be used as a solvent to act as proton acceptor and shift the equilibrium point toward the formation of the desired derivative:

$$RNH_2 + CH_3COCl \rightarrow CH_3CONHR + H^+ + Cl^-$$

$$ROH + CH_3COCl \rightarrow CH_3COOR + H^+ + Cl^-$$

In the absence of a proton acceptor, such as pyridine or dimethylaniline, tertiary alkyl alcohols are largely converted by acetyl chloride to the alkyl chlorides instead of to the acetate esters.

As both acetyl chloride and acetic anhydride react fairly rapidly with water, they cannot be used in presence of water or with carbon compounds that contain considerable amounts of moisture. Under certain conditions, acetic anhydride may be used in presence of water for the acetylation of reactive compounds. The hydroxy or amino compound is suspended in a solution containing a slight excess of alkali; crushed ice is added and, when the mixture is cold, the acetic anhydride is added and the solution is vigorously shaken.

Benzoylation is generally more advantageous than acetylation; for one thing, benzoyl chloride is very slightly attacked by water at room temperature. In addition, the benzoyl derivatives have higher melting points and as a rule better crystallizing properties than the acetyl derivatives. The procedure generally used is to add a slight excess of benzoyl chloride to the hyxroxy or amino compound, then add 10 per cent aqueous sodium hydroxide solution, and shake the mixture vigorously. The hydrogen chloride formed in the reaction is removed by the alkali. The solution is kept at first cold and then slightly warmed to hydrolyze

the excess of benzoyl chloride. This method is known as the *Schotten-Baumann reaction.* The benzoyl derivatives nearly always crystallize well. The product is recrystallized to remove adsorbed and occluded impurities. If the derivative does not crystallize well, then a substituted benzoyl chloride is used, such as *p*-nitrobenzoyl chloride or 3, 5-dinitrobenzoyl chloride. Both of the nitro-substituted benzoyl chlorides are solids and must be heated with the hydroxy or amino compound. If the reaction is slow, boiling in presence of pyridine is beneficial. Benzenesulfonyl chloride is used under the same conditions as benzoyl chloride. In addition to the few examples given below, examples of acylation will be found on pages 222-4 and 257-8.

8.27 Benzoylation of an amine. Place in an 8-inch test tube 0.1 ml of *o*-toluidine, 0.2 ml of benzoyl chloride, and 4 ml of 10 per cent sodium hydroxide in the order given. Close the tube with a No. 5 or No. 6 solid rubber stopper and shake vigorously for 1 minute and then at intervals for 10 minutes. Add 6 ml of water and filter the benzo-*o*-toluidide that separates out. Recrystallize from alcohol. The yield is 150–180 mg of crystals which melt at 143°.

8.28 Benzoylation of a phenol. Use the same proportion of reagents and the same procedure as in experiment 8.27. Dissolve the crude phenyl benzoate in 5 ml of methanol, filter the hot solution, and add water dropwise until a permanent cloudiness occurs. Warm the solution until it becomes clear; then cool. Filter the solid and wash with 25 per cent methanol. The yield is 150–180 mg of crystals, which melt at 69°.

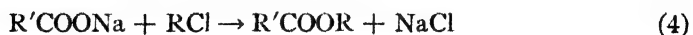
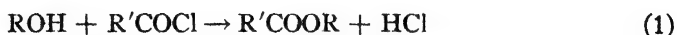
8.29 Acetylation of β-naphthol. Place in an 8-inch test tube 100 mg of β-naphthol, 0.4 ml of acetic anhydride, and 1 drop of sulfuric acid. Heat gently for 3 minutes and then allow to cool. Add 3–4 ml of water and stir the oil by means of a glass rod until it solidifies. Filter, wash the solid with cold water, and crystallize from methanol as directed in 8.28. The yield is 100–120 mg of crystals, which melt at 71–72°.

Esterification. Formation of esters may take place as a result of any of the following reactions:

$$ROH + R'COCl \rightarrow R'COOR + HCl \quad (1)$$

$$ROH + (R'CO)_2O \rightarrow R'COOR + R'COOH \quad (2)$$

$$ROH + R'COOH \rightarrow R'COOR + H_2O \quad (3)$$

$$R'COONa + RCl \rightarrow R'COOR + NaCl \quad (4)$$

Equations (1) and (2) represent acetylations of alcohols discussed in the preceding section (page 180). Equation (3) represents the reaction be-

tween an acid and an alcohol. Although this method is the one most widely used for macro preparative work, it is not very satisfactory for identification purposes, since it does not lend itself to the rapid preparation of small amounts of esters containing a minimum amount of impurities.

The reaction between the sodium salt of a carboxylic acid and a halide shown in Equation (4) is well adapted to the preparation of esters for identification work from carboxylic acids containing water. Phenacyl chloride ($C_6H_5COCH_2Cl$), or bromide, and *p*-nitrobenzyl chloride ($NO_2C_6H_4CH_2Cl$) are the halides most commonly used for the preparation of many solid esters.

8.30 p-Nitrobenzyl benzoate. Place into an 8-inch test tube 200 mg of benzoic acid and 5 ml of methanol. Add 1 drop of phenolphthalein. Add dropwise 10 per cent sodium hydroxide solution until the acid has been neutralized and the color of the solution is just pink. Add 2–3 drops of 5 per cent hydrochloric acid so that the pink color of the solution is discharged. Add 200 mg of *p*-nitrobenzyl chloride and a small boiling stone. (**Caution:** In weighing and transferring *p*-nitrobenzyl chloride, avoid contact with the skin.) Arrange the tube for reflux and boil gently for 2 hours.

Cool, add 1 ml of water, and scratch the sides of the tube. After 15–20 minutes filter the ester and wash it (1) twice with 4 ml of 5 per cent sodium hydroxide solution and (2) twice with 4 ml of water. Dissolve the ester in 6–8 ml of hot methanol, filter, and add water to the hot filtrate until a cloudiness appears; heat the tube until the cloudiness disappears. Cool in running water, and scratch the inner surface of the tube with a glass rod. Filter and wash the ester with 1–2 ml of 50 per cent methanol. The yield is 100–120 mg of crystals, which melt at 89°.

Alkylation and arylation. The introduction of alkyl and aryl radicals into carbon compounds may be accomplished in a variety of ways. The discussion in this section will be restricted to a few types of alkylation and arylation that are valuable in identification work. From a broad point of view, the Wurtz-Fittig synthesis, the Friedel-Crafts reaction, and the formation of keto esters, Grignard reagents, amines, and other compounds may often be classified as alkylations and arylations. For example, the formation of dimethylaniline and diphenylamine from aniline may be regarded as examples of alkylation and arylation of a primary amine.

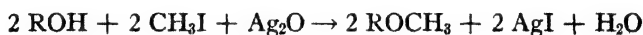
Alkylation of naphthols is of use in the identification of alkyl halides. β-Naphthol reacts with alkyl halides to form an ether in the presence of sodium hydroxide, as shown in the following equation:

$$\underset{\beta\text{-Naphthol}}{C_{10}H_7OH} + \underset{\text{Alkyl halide}}{XR} \rightarrow \underset{\text{Alkyl-}\beta\text{-naphthyl ether}}{C_{10}H_7OR} + HX$$

Alkyl-β-naphthyl ethers are solids. The same type of reaction occurs under appropriate conditions with all hydroxy compounds; for example, alcohols do not form alkoxides easily with sodium hydroxide, but do so with sodium metal. Therefore, for the preparation of ethers, sodium metal is first reacted with the alcohol and then treated with the alkyl halide.

The methylation of sugars is another instance of alkylation that is of interest in identification work. A mixture of dimethyl sulfate and the sugar is treated with an alkaline solution under conditions that insure thorough mixing and safety from the *poisonous* vapors of dimethyl sulfate.

Another method of introducing the methyl group that is safer for beginners is to shake the hydroxy compound (sugar or phenol) with a mixture of silver oxide or silver carbonate and methyl iodide:

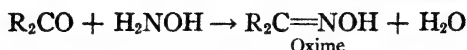
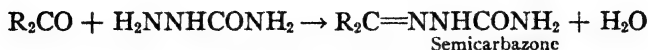
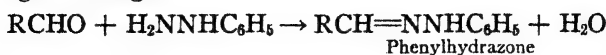
$$2\ ROH + 2\ CH_3I + Ag_2O \rightarrow 2\ ROCH_3 + 2\ AgI + H_2O$$

8.31 Methyl-β-naphthyl ether. In a test tube provided with a reflux condenser place 4 ml of methanol, 200 mg of β-naphthol, 1 ml of 10 per cent sodium hydroxide solution, and 0.2 ml of methyl iodide. Warm for 20 minutes in a water bath; then add 5 ml of water and filter the crystals, washing with water. The ether may be recrystallized from alcohol.

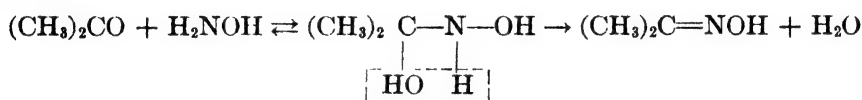
Condensations. The term condensation is used at times in a general manner to designate any reaction that involves uniting one carbon atom to another. The term is also employed in a restricted sense to designate certain types of reactions in which a more complex substance is obtained from one or two simpler substances, usually accompanied by elimination of water or some other simple inorganic compound. Aldehydes and ketones will react with other aldehydes, acids, esters, and amino compounds, to form more complex substances. Many of these reactions are named after the investigator or with reference to the product, followed by the word condensation, synthesis or reaction. The names *Claisen condensation*, *Perkins synthesis or reaction*, *Schiff's reaction*, *Knoevenagel reaction*, *benzoin condensation*, *aldol condensation*, *Cannizzaro reaction*, *Tischtschenko reaction*, for instance, are used to designate types of this reaction. Of particular interest in identification work is the condensation of carbonyl compounds with semicarbazide, phenylhydrazine and hydroxylamine, all of which may be regarded as substituted ammonia compounds. As shown in the equations, condensation involves the

elimination of the carboxyl oxygen and two amino hydrogen atoms, which results in the formation of water and leads to a double-bonded carbon-nitrogen linkage.

$$RCHO + H_2NNHC_6H_5 \rightarrow \underset{\text{Phenylhydrazone}}{RCH{=}NNHC_6H_5} + H_2O$$

$$R_2CO + H_2NNHCONH_2 \rightarrow \underset{\text{Semicarbazone}}{R_2C{=}NNHCONH_2} + H_2O$$

$$R_2CO + H_2NOH \rightarrow \underset{\text{Oxime}}{R_2C{=}NOH} + H_2O$$

The mechanism of such a reaction is assumed to consist in addition of the amino compound to the carbonyl group, followed by elimination of water:

$$(CH_3)_2CO + H_2NOH \rightleftarrows (CH_3)_2\underset{\boxed{HO\quad H}}{C{-}N{-}OH} \rightarrow (CH_3)_2C{=}NOH + H_2O$$

The experimental details for the preparation of semicarbazones and phenylhydrazones are given on pages 245–8.

8.32 Benzaldoxime. Place in a 6-inch tube 150 mg of hydroxylamine hydrochloride, 1.5 ml of 10 per cent sodium hydroxide solution, and 2 ml methanol. Add 0.2 ml of benzaldehyde. Place a solid rubber stopper into the mouth of the tube and shake vigorously for about 1 minute; allow to stand for 1 hour with occasional shaking. If the odor of benzaldehyde has not disappeared, warm the tube for 15–20 minutes. Add dilute acid until all the alkali has been neutralized. Cool and filter the solid. Wash with water and recrystallize from methanol.

Note: For the preparation of oximes from ketones, see Section 11.9, page 248.

Hydrolysis. Any reaction of an organic compound with water that leads to a cleavage of the molecules and addition of hydrogen and hydroxyl from water to the groups resulting from such cleavage is commonly called hydrolysis:

$$\underset{\text{Acetamide}}{CH_3CONH_2} + HOH \rightarrow CH_3COOH + NH_3 \quad (1)$$

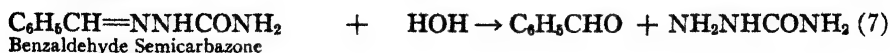
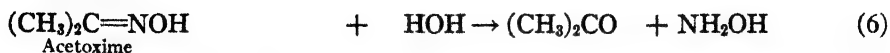
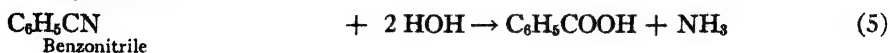
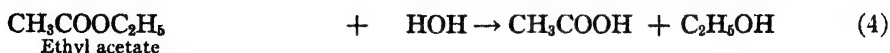
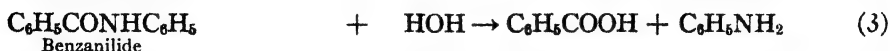
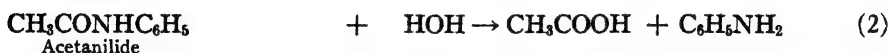
$$\underset{\text{Acetanilide}}{CH_3CONHC_6H_5} + HOH \rightarrow CH_3COOH + C_6H_5NH_2 \quad (2)$$

$$\underset{\text{Benzanilide}}{C_6H_5CONHC_6H_5} + HOH \rightarrow C_6H_5COOH + C_6H_5NH_2 \quad (3)$$

$$\underset{\text{Ethyl acetate}}{CH_3COOC_2H_5} + HOH \rightarrow CH_3COOH + C_2H_5OH \quad (4)$$

$$\underset{\text{Benzonitrile}}{C_6H_5CN} + 2\,HOH \rightarrow C_6H_5COOH + NH_3 \quad (5)$$

$$\underset{\text{Acetoxime}}{(CH_3)_2C{=}NOH} + HOH \rightarrow (CH_3)_2CO + NH_2OH \quad (6)$$

$$\underset{\text{Benzaldehyde Semicarbazone}}{C_6H_5CH{=}NNHCONH_2} + HOH \rightarrow C_6H_5CHO + NH_2NHCONH_2 \quad (7)$$

Equations 1–7 represent the important types of hydrolyses that are met in identification work. Among other hydrolytic reactions are the decomposition of anhydrides and the hydrolysis of polysaccharides and of halogen compounds. The rate of hydrolytic reactions is accelerated and the equilibrium point shifted to the right, as shown in the above equations, by heating the compounds with aqueous solutions of acids or bases. The conditions and the proper catalyst to use depend on the type of compound to be hydrolyzed. Solutions of bases are more effective for the esters. The following examples illustrate some of the conditions.

8.33 Hydrolysis of ethyl benzoate. Place 0.5 ml of ethyl benzoate and 3 ml of 10 per cent sodium hydroxide solution in a test tube provided with a microcondenser. Add 2 boiling stones and boil gently, by means of a small flame, for 30 minutes until the ester layer disappears. The resulting solution will contain the alcohol and the sodium salt of the acid. If it is desired to separate the alcohol, the liquid is distilled until 2 ml of distillate has been collected; otherwise, the solution is cooled and acidified with hydrochloric acid. Benzoic acid then separates from the solution. The crystals are filtered and dried.

8.34 Hydrolysis of benzophenoxime. Arrange an 8-inch tube for reflux and add 200 mg of benzophenoxime and 4 ml of 6 *N* hydrochloric acid solution. Boil for 15 minutes. Cool and add 5 ml of ether. Shake well and separate the ether layer. Distil off the ether and use the residue to prepare the 2, 4-dinitrophenylhydrazone as described on page 247.

8.35 Hydrolysis of benzamide. Use procedure 8.33.

8.36 Hydrolysis of aceto-p-toluidide. Place into an 8-inch test tube arranged for reflux 200 mg of aceto-*p*-toluidide, 4 ml of 6 *N* hydrochloric acid solution, and 2 boiling stones. Boil gently for 10 minutes. Render the solution slightly alkaline and cool it in an ice bath. Filter the crystals of *p*-toluidine. Upon evaporation the filtrate yields sodium acetate, which may be used for the preparation of the *p*-nitrobenzyl ester.

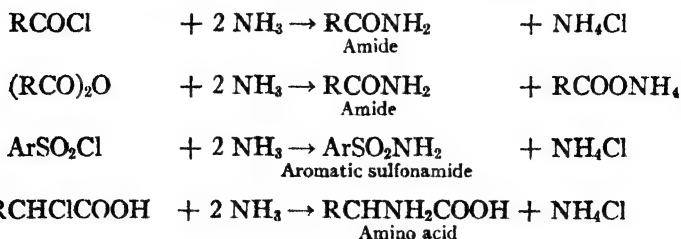
Amination. The most important methods for the introduction of the amino group are the reduction of nitro compounds and the ammonolysis of halogen compounds. Esters, hydroxy compounds, and sulfonic acids may undergo ammonolysis, but the application of these methods is restricted.

The reduction of nitro groups has been discussed on pages 168–170 and illustrated in procedures 8.6, 8.7, 8.8, and 8.12–8.14. The ammonolytic reactions that are of use in identification work are the ammonolysis of acid chlorides, acid anhydrides, sulfonyl chlorides and halogen acids:

$$RCOCl + 2\,NH_3 \rightarrow \underset{\text{Amide}}{RCONH_2} + NH_4Cl$$

$$(RCO)_2O + 2\,NH_3 \rightarrow \underset{\text{Amide}}{RCONH_2} + RCOONH_4$$

$$ArSO_2Cl + 2\,NH_3 \rightarrow \underset{\text{Aromatic sulfonamide}}{ArSO_2NH_2} + NH_4Cl$$

$$RCHClCOOH + 2\,NH_3 \rightarrow \underset{\text{Amino acid}}{RCHNH_2COOH} + NH_4Cl$$

The compound to be ammonolyzed is usually mixed with a large excess of concentrated aqueous ammonia and allowed to stand at room temperature for several hours; it is then heated to 60° to complete the reaction and drive off the excess of ammonia. Such a procedure is fairly satisfactory with acyl, aroyl, and aryl sulfonyl chlorides, which react fairly rapidly so that the formation of secondary (R_2NH) and tertiary (R_3N) amino compounds is kept at a minimum. With esters and halogen compounds, however, excess of 40–50 moles of ammonia is required for a good yield of the primary amino compound.

A better process of ammonolysis is through the use of concentrated solutions of ammonium carbonate and ammonia, which obviates the necessity for a large excess of ammonia. The presence of the carbamate ion and the lowered *p*H of the ammonolytic medium keep side reactions at a minimum.[6] Procedure 8.37 illustrates this method. In the ammonolysis of semimicro quantities of acyl halides, the use of aqueous ammonolytic media is not practical, because the lower amides are soluble. When 100–200 mg of an acyl halide that has less than 8 carbon atoms are involved, it is advisable to use a solution of ammonia in benzene or other inert solvent, such as isopropyl ether. Procedure 8.38 illustrates this method.

When the compound to be ammonolyzed reacts slowly and also is insoluble in water, alcoholic ammonolytic media should be used. Methanol is saturated with ammonia at 20° or until it absorbs 15–18 per cent ammonia. Sufficient ammonium carbonate to equal the weight of ammonia in the solution is then added. The resulting ammonium carbamate dissolves, while the bicarbonate remains undissolved. The mixture, however, may be used directly like the aqueous system described in procedure 8.36.

8.37 dl-Alanine. Place into an 8-inch test tube 3 ml of concentrated aqueous ammonia and 1 g of powdered ammonium carbonate. Place the tube in a water bath and warm at 40° for 15–20 minutes. Cool to 25° and then add 500 mg of α-bromopropionic acid. Stopper and put the

[6] Cheronis and Spitzmueller, *J. Org. Chem.*, **6**, 349 (1941).

tube aside for 24 hours at room temperature. Remove the stopper, place in a water bath, and heat gradually to expel the ammonia and carbon dioxide (use hood). Continue heating until the liquid in the tube has been reduced to a volume of about 1 ml. Add 2–4 ml of methanol and cool the tube for 1 hour. Filter the alanine crystals and wash twice with two 1-ml portions of methanol. Transfer the crystals to an 8-inch test tube and add 5 ml of methanol; let stand for 30 minutes with occasional stirring. Filter, wash once with methanol, and remove the solid to a drying disc. The yield is about 200–250 mg. The product should give only a faint opalescence when its solution is tested with acidified silver nitrate.

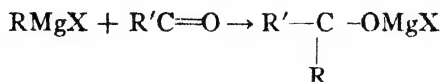
8.38 Ammonolysis of an acyl chloride. To 10 ml of dry benzene saturated with ammonia contained in an 8-inch test tube, add 0.2 ml of butyryl chloride. Cork the tube and allow it to stand in the cold for 15 minutes. Pour the mixture through a fluted filter paper and wash the residue of ammonium chloride with 2–3 ml of dry benzene. Cautiously evaporate the benzene from a water bath. About 125–150 mg of the amide are obtained; the crystals melt at 115°.

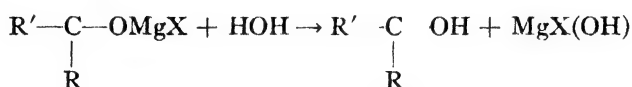
8.39 Ammonolysis of an ester. Place in an 8-inch test tube 1 ml of concentrated aqueous ammonia, 500 mg of powdered ammonium carbonate, and 1 ml of ethanol. Warm at 40° for 20 minutes and then cool to 20°. Add 300 mg of ethyl malonate. Allow to stand for 1 hour with occasional shaking. Heat the tube at 60° for 15–20 minutes and then at 80° for 5 minutes, to drive off the alcohol and decompose the ammonium carbonate. Add 2 ml of water and cool. Filter the solid and wash it with 1 ml of cold water. The yield is 100–125 mg of malonamide, melting at 170°.

Grignard reagents. The action of either alkyl or aryl halides upon magnesium metal in presence of anhydrous ether forms an organometallic compound that may be represented by the general formula R-MgX, where R stands for an organic radical and X for a halogen atom. For an extensive discussion of the structure of this type of organometallic compound, the reader is referred to the literature.[7] These compounds, R : Mg : X, may be considered very unstable structures and usually react so as to undergo cleavage into $(R)^-$ and (Mg^+X). Therefore, the formation of Grignard reagents may be regarded as involving a partial reduction of an organic halogen compound. The magnesium atom, in forming a bond with the carbon atom, contributes to it by the sharing of its two electrons. This bond is easily disrupted, with the formation of an organic negative ion $(R)^-$ and an inorganic positive (Mg^+X) ion.

[7] Gilman, *Organic Chemistry*, 2nd Ed., John Wiley and Sons, Inc., 1943, pp. 495–520.

When the Grignard reagent reacts with compounds that have an unsaturated (oxygen-carbon, nitrogen-carbon, sulfur-carbon, etc.) bond, the organic part, R, adds to the carbon atom, and the inorganic part, MgX, adds to the oxygen, nitrogen, or sulfur atom:

$$RMgX + R'C{=}O \rightarrow R'{-}\underset{\displaystyle R}{\underset{|}{C}}{-}OMgX$$

The addition product reacts with water or with any reagent capable of giving up a hydrogen ion; the latter attaches itself to the oxygen (or nitrogen or sulfur):

$$R'{-}\underset{\displaystyle R}{\underset{|}{C}}{-}OMgX + HOH \rightarrow R'{-}\underset{\displaystyle R}{\underset{|}{C}}{-}OH + MgX(OH)$$

The Grignard reagent is capable of being used for the preparation of alcohols, ketones, carboxylic acids, and other types of organic compounds. The present brief discussion is confined to the most important uses of the Grignard reagent in identification work.

The preparation of the Grignard reagent for semimicro work is illustrated in the experimental procedures that follow. Moisture must be excluded, both from the reagents and the apparatus. For semimicro work with only 100–200 mg of reagents involved, it is possible to eliminate all special apparatus and a number of the classical precautions that are usually taken in the preparation of the Grignard reagent. Stirring is not necessary in the reaction of 50–100 mg of magnesium metal. The reaction of this amount of metal usually takes about 5–10 minutes. The apparatus shown in Figure 64 consists of an 8-inch or 6-inch tube provided with a stopper, which holds a tightly fitting condenser and a calcium chloride tube. Ethyl ether for the preparation of Grignard reagents must contain a minimum amount of moisture; a small piece of freshly cut sodium added to the dry ether must not give rise to evolution of minute bubbles of gas from the metallic surface.

Absolute ether for semimicro work may be kept in a 250-ml Erlenmeyer flask containing a few pieces of fused calcium chloride and of sodium cuttings. When needed, 5–7 ml are poured into the reaction tube through a clean dry funnel fitted with a small plug of cotton. The magnesium turnings should be clean and without a coating of oxide. It is advisable to cut the metal into small pieces so as to expose some fresh and clean surface. The purity of the halide is at times of vital importance. Traces of impurities may exert a retarding effect, in which case the reaction either does not start or is sluggish. On the other hand, in the

experience of the authors, technical grades of some halides have given good results.

The use of other solvents, such as isopropyl and *n*-butyl ethers, pyridine, and others, in place of ethyl ether is not recommended for semimicro work. For instance, 0.005 moles each of magnesium and methyl iodide (0.32 ml) shows no reaction after 15 minutes if isopropyl ether is used, and only a meager reaction when pyridine is used.

The most important uses of the Grignard reagent in identification work are summarized by the equations below:

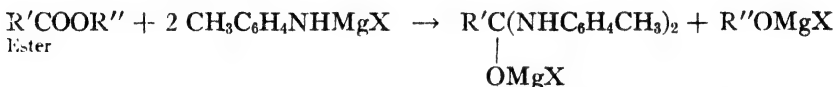
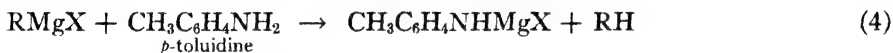
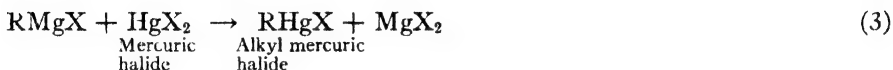
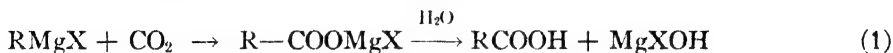
$$RMgX + CO_2 \rightarrow R{-}COOMgX \xrightarrow{H_2O} RCOOH + MgXOH \quad (1)$$

$$RMgX + \underset{\text{Phenyl isocyanate}}{C_6H_5{-}NCO} \rightarrow C_6H_5{-}NCOMgX \xrightarrow{H_2O} C_6H_5{-}NHCOR + MgXOH \quad (2)$$

$$RMgX + \underset{\text{Mercuric halide}}{HgX_2} \rightarrow \underset{\text{Alkyl mercuric halide}}{RHgX} + MgX_2 \quad (3)$$

$$RMgX + \underset{p\text{-toluidine}}{CH_3C_6H_4NH_2} \rightarrow CH_3C_6H_4NHMgX + RH \quad (4)$$

$$\underset{\text{Ester}}{R'COOR''} + 2\ CH_3C_6H_4NHMgX \rightarrow \underset{\displaystyle |\atop \displaystyle OMgX}{R'C(NHC_6H_4CH_3)_2} + R''OMgX$$

$$\underset{\displaystyle |\atop \displaystyle OMgX}{R'C(NHC_6H_4CH_3)_2} + 2\ HCl \rightarrow \underset{p\text{-toluidide}}{R'CONHC_6H_4CH_3} + CH_3C_6H_4NH_3Cl + MgXCl$$

Equation (1) represents the identification of a halide by its conversion to the Grignard reagent followed by carboxylation. The carboxylic acid is identified by its melting point, if it is a solid, or by preparation of a derivative, if it is a liquid.

Equation (2) represents the reaction of a Grignard reagent with phenyl isocyanate to form an anilide; this reaction may be used for the identification of a halide. In the case of a primary alkyl halide, the Grignard reagent may be converted to the corresponding alkylmercuric halide by treatment with a mercuric halide, as shown by Equation (3). Equation (4) represents the identification of the acidic portion of an ester by reacting it with a Grignard reagent and *p*-toluidine, to form the *p*-toluidide. The procedures are described on pages 191–2, 233, 282–3.

8.40 Pure ether for Grignard reagents. The following directions are for the rapid preparation of 10–50 ml of dry ether required in making semimicro quantities of Grignard reagents. For the preparation of larger quantities required in organic laboratories, consult a standard laboratory manual. The impurities in commercial ether are water and ethanol.

Although ether and water are regarded as immiscible liquids, water dissolves in ether to the extent of 1.35 per cent.

Place 50–100 ml of ether in a 250-ml Erlenmeyer flask. Wash with 20–25 ml of water containing 0.5 g of ferrous sulfate and a few drops of concentrated sulfuric acid (see page 236). Separate the ether and place it in a dry flask. Add 4–5 g of fine granular anhydrous calcium chloride, stopper securely, and shake at intervals for 10 minutes; cool the flask in tap water and release the stopper after each shaking. Calcium chloride

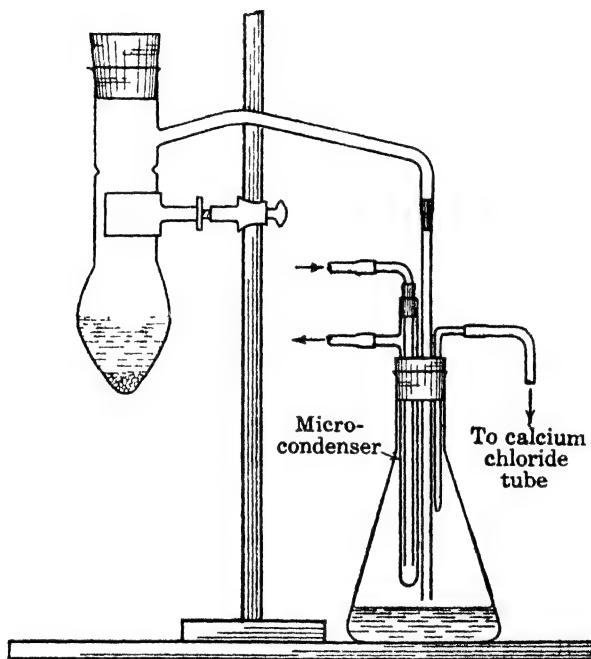



FIGURE 63

Semimicro Apparatus for Preparation of Absolute Ether

removes most of the alcohol and water. Filter the ether through a large, fluted filter paper into a dry, clean flask or bottle. Add about 2 g of sodium cuttings. Close the bottle or flask with a paraffined cork holding a calcium chloride tube, to allow escape of hydrogen. The tip of the calcium chloride tube is drawn out to a fine point so as to reduce the opening. Allow to stand for 2–3 hours. Place 1 g of sodium cuttings and 20 ml of the ether into a large distilling tube (straight or pear-shaped) attached for distillation as shown in Figure 63. The receiving flask contains 2–3 small pieces of fused calcium chloride and serves for permanent storage of the dry ether. The two-hole rubber stopper fits

tightly into the flask carrying the delivery tube and L outlet glass tube; the latter is connected by means of a long rubber tubing that reaches well below the bench toward the floor and has a calcium chloride tube at the end. Raise a beaker of hot water (heated at another part of the bench) until the ether begins to distil. Adjust the temperature to about 50° by adding hot or cold water and continue the distillation until about 5 ml of ether are left in the distilling tube. Recharge the distilling tube and continue the distillation. Discontinue the distillation before the residue in the distilling tube becomes dry. The distillation of ether, which contains peroxides because of exposure to light and air, involves a danger of explosion if the distillation is allowed to proceed to dryness. The presence of peroxides is detected by adding 2 ml of ether to a mixture of 3 ml of water, 2 ml of starch suspension, and 0.5 ml of potassium iodide solution. Shake and, if a blue color does not appear immediately, add a drop of dilute sulfuric acid and shake again. Ether that contains peroxides liberates iodine from an acid solution of potassium iodide. Although the danger is minimized when only small quantities of ether are involved, it is considered important to caution the beginner.

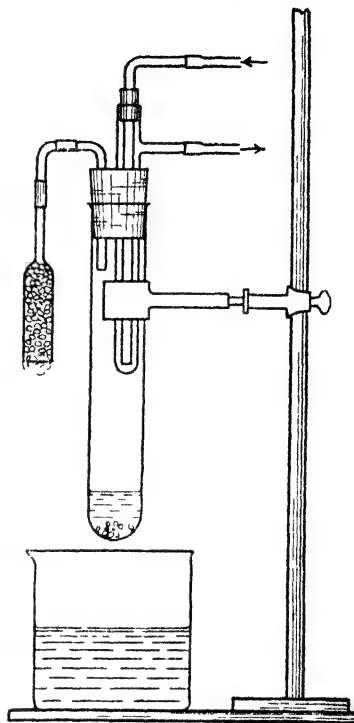



FIGURE 64

Semimicro Apparatus for Preparation of Grignard Reagent

The ether prepared as described above is anhydrous and practically free from other impurities. If it is not used within a day, it should be kept in the dark and stoppered with a well-fitting cork covered with a metal foil. If the quantity of dry ether prepared is only 10–15 ml or sufficient for but one preparation, it may be distilled directly into an 8-inch tube.

8.41 Benzoic acid from bromobenzene. Clean an 8-inch tube well and dry it by heating strongly over a flame to drive all the moisture out. Cork the tube while hot and allow it to cool.

Place 120 mg of magnesium in the tube and arrange apparatus as shown in Figure 64. The microcondenser is wiped off with a perfectly dry cloth; then the cork, which holds the condenser and the calcium

chloride tube, is inserted in the mouth of the tube. The cork has two holes and fits tightly into the mouth of the tube. Raise the cork momentarily and add 800 mg of bromobenzene in 5 ml of absolute ether and a crystal of iodine. The reaction starts within a few minutes and requires 5–10 minutes for completion. If the reaction is too slow in starting, raise a small beaker containing warm water (50–60°) over the outside of the tube for about a minute. If, after the color of iodine disappears, the reaction proceeds very slowly and requires constant heating, moisture is present in the apparatus or in the reagents. The carbonation of the Grignard reagents is effected by adding small pieces of dry ice. About 2–3 g of dry ice are broken into small pieces, the size of almonds. The tube with the Grignard reagent is then placed in the hood; after wiping off each piece of ice with a dry cloth, drop it into the tube. The reaction is vigorous and most of the ether may be evaporated with the excaping carbon dioxide. Stir the resinous mass by means of a glass rod and allow to stand for 5 minutes. Decompose the carbonated resinous mass with a mixture of 2 ml concentrated hydrochloric acid and 3 g of ice.

When the decomposition is complete and practically all the residual magnesium has dissolved, add 5 ml of ether and extract the mixture. The extraction is repeated once or twice if the acid is appreciably soluble in water, as in the case of the lower, open-chain acids. Combine the ether extracts in a tube and shake with 3 ml of 5 per cent sodium hydroxide. The acid passes from the ether to the aqueous layer as it forms the sodium salt; wash the ether with 1 ml of water and withdraw the resulting aqueous layer, uniting it with the alkaline solution. Acidify carefully the solution containing the sodium salt. Cool, filter, and wash with water the benzoic acid that separates out. The yield is 500–550 mg of crystals melting at 118–120°. The acid may be crystallized either from an alcohol water mixture or by solution in sodium hydroxide followed by precipitation with acid.

8.42 Phenylacetic acid. Use 600 mg of benzyl chloride, 120 mg of magnesium metal, and 5 ml of ether. The same procedure is followed as in the preparation of benzoic acid. The solubility of phenylacetic acid in water is much greater than that of benzoic acid; hence care should be taken not to use excessive amounts of water. Save all filtrates and, if the yield is poor, evaporate them to obtain an additional amount of the acid.

8.43 n-Caproic acid. Use 1 g of *n*-amyl bromide, 140 mg of magnesium, and 5 ml of ether. After carbonation and decomposition of the addition product, the alkaline layer from ether extraction is cooled and

carefully acidified, and then extracted with three 5-ml portions of ether. The ethereal solution is dried with 1 g of calcium chloride and the ether is distilled directly from the large distilling tube until all of it is driven off. The residue is used to prepare the *p*-toluidide after conversion to the acyl chloride. Use the procedure given in 9.3, page 210.

Molecular compounds. A number of organic substances form relatively stable molecular compounds with *picric acid*, *trinitrobenzene*, *α-naphthylamine*, and other reagents. For example, naphthalene dissolved in alcohol and treated with a saturated solution of picric acid forms a difficultly soluble picrate, $C_{10}H_8 \cdot C_6H_2(NO_2)_3OH$; this molecular compound crystallizes from ethyl acetate in yellow prisms or plates, and from ethyl alcohol in monoclinic prisms and needles, and melts at 149°. This derivative, therefore, may be used for the identification of naphthalene. Insoluble picrates that may be used as derivatives are formed by other polynuclear hydrocarbons, phenolic ethers, and tertiary amines. Many alkyl halides with thiourea and picric acid form *S-alkylisothiourea picrates.* α-Naphthylamine forms molecular compounds with 3,5-dinitrobenzoates and may be used in the identification of alcohols (page 218).

The theories respecting the type of bond that exists between molecules in compounds of this type are inadequate, and therefore no generalization can be made. Some of the molecular compounds, such as the *S*-alkylisothiourea picrates, are sufficiently stable to permit crystallization from a hot solvent; others, like most of the picrates that are formed by aromatic hydrocarbons, are decomposed by hot solvents or by exposure to the air. The formation of molecular compounds is favored by: (a) increase in the number of nitro groups present in the nitro compound; (b) presence of electron-attracting groups like CN and $COCH_3$ in the nitro compound; (c) presence of electron-repelling groups like CH_3, OH and NH_2 in the reacting substance. The presence of methyl groups in the nitro compound or of unsaturated linkages in the substance reacting with it does not favor the formation of stable molecular compounds. The bonding of the molecules in such "addition" compounds has been explained on the basis of oxonium-salt formation and hydrogen bonds. Procedures for experiments on the formation of molecular compounds are given on pages 264, 281–2, and 314–5. References on the nature of molecular compounds are given on pages 241 and 318.

Index to Preparation of Derivatives

CHAPTER 9

Preparation of Derivatives

THE preparation of suitable derivatives is the last and conclusive step in the identification of an organic compound. Hitherto the identification has been based on: (a) preliminary tests; (b) determination of melting point or boiling point, refractive index, and other physical constants; (c) determination of the elements present; (d) solubility data; and (e) functional-group reactions. On the basis of this information a list of compounds is prepared, and the one that best fits the data is then selected as the probable compound. As previously stated, the final and conclusive step leading to proof of the identity of the unknown is the preparation of suitable derivatives. If the derivatives prepared melt within 1–2° of the melting point given in the literature for the same derivatives of the probable compound, the identification is regarded as conclusive. Further confirmation is obtained by the determination of the melting point of a mixture consisting of one of the derivatives prepared from the unknown and the same derivative prepared from a pure sample of the compound identified as the unknown. The melting point of such a mixture should not vary more than 1° from the melting point of either component alone. If the unknown is a solid, a mixture of the unknown itself and the compound identified as the unknown may be used for the determination of the mixed melting point.

Requirements for useful derivatives. Most organic compounds undergo a number of reactions that give rise to other compounds which may be used as *derivatives*. For example, an aldehyde may be oxidized to an acid, reduced to an alcohol, or converted into an oxime, phenylhydrazone, or semicarbazone. Although theoretically all these reactions may be used to prepare derivatives for the characterization of an aldehyde, practical considerations demand that a derivative must fulfill certain requirements in order to be suitable for characterization purposes. These requirements are:

1. The derivative should be a solid, melting, if possible, above 50° and below 250°. If the derivative is an oil, it cannot be purified in small quantities; as a rule organic crystalline compounds melting below 50° do not crystallize well and in such cases they have a tendency to separate as oils. A derivative melting between 100–200° is preferable (other fac-

tors being equal) to a derivative melting much above 200°; the determination of melting points much above 200° is more difficult and requires considerable care in ascertaining the thermometer correction to be ap plied.

2. The derivative should have a melting point that is quite different from that of the original compound from which it is prepared; further, the melting point of the derivative should be more than 5° apart from the derivatives of closely related compounds. In the example cited on page 153. let us consider an unknown which, on the basis of tests, is tentatively identified as propionic acid. In the selection of the derivatives to be prepared, reference is made to Table 1, page 358, and it is found that the anilide of propionic acid melts at 105° (103°), whereas the anilide of isobutyric acid, a closely related acid and one of the possibilities, melts at 105°. Note that two values are recorded for the anilide of propionic acid, indicating that two or more values are found in the literature for the melting point of this derivative. On the other hand, the *p*-toluidide of propionic acid melts at 124°, whereas that of isobutyric melts at 107° (104°); therefore the *p*-toluidide in this particular case is a much more suitable derivative than the anilide.

3. The reaction by which the derivative is made should be complete within 30 minutes, should be subject to few, if any, side reactions, and should afford a good yield.

4. The reagents used in the preparation of a derivative should be readily available.

5. The derivative should be readily purified; it should be slightly soluble in some common solvent in the cold and somewhat soluble at the boiling point of the solvent. More specifically, the ratio of the solubility at room temperature to that at the boiling point of the solvent should be more than 1:5.

These considerations demand care and thought in the selection of an appropriate derivative. Although in this text certain derivatives are recommended, it is to be understood that these recommendations are general and that each case must be considered separately by the person doing the investigation. The selection of the appropriate derivative is even more important when semimicro quantities are involved, because the quantity of the derivative to be prepared seldom exceeds 100–200 mg.

The number of derivatives described in the literature as suitable may be rather large in some groups of compounds. For example, as shown in Table V, a considerable number of derivatives are available for the identification of carboxylic acids, alcohols, and carbonyl compounds. Since Table V represents only a partial list of the derivatives proposed in the

TABLE V

Partial List of Derivatives Useful for Identification of Carboxylic Acids, Alcohols, and Carbonyl Compounds

Carboxylic Acids	Alcohols	Carbonyl Compounds
p-Toluidides	3, 5-Dinitrobenzoates	Semicarbazones
Anilides	α-Naphthylurethans	2, 4-Dinitrophenylhydrazones
Amides	Phenylurethans	*p*-Nitrophenylhydrazones
p-Bromoanilides	3, 5-Dinitrophenylurethans	Phenylhydrazones
Methylenebisanilides	*p*-Xenylurethans	*o*- and *p*-Chlorobenzohydrazones
p-Nitrobenzyl esters	*p*-Nitrophenylurethans	3-Nitrobenzohydrazones
p-Phenylphenacyl esters	4-Iodobiphenylurethans	Diphenylhydrazones
p-Chlorophenacyl esters	*p*-Nitrobenzoates	Nitroguanylhydrazones
p-Bromophenacyl esters	Hydrogen-3-nitrophthalates	*p*- and *m*-Tolylsemicarbazones
Benzimidazoles	Hydrogen phthalates	1- and 2-Naphthylsemicarbazones
Phenylhydrazides	*p*-Nitrobenzyl phthalates	Methone derivatives
Benzylammonium salts	tert-Alkylhydrogen tetrachlorophthalates	Benzothiazoles
S-Benzylthiouronium salts	Xanthates	Oximes
	Alkyl-3, 5-dihydroxybenzoates	

literature, the authors considered it necessary, for the purposes of this work, to select *recommended derivatives* for beginners on the basis of actual tests. In the tables of derivatives (pages 358–458), the recommended derivatives are listed in the first two or three columns and are appropriately marked. For example, in the case of carboxylic acids, alcohols, and carbonyl compounds, the recommended derivatives are the first two listed in each column of Table V.

Recommended derivatives. The preparation of the recommended derivatives is described in chapters 9–13 in detail. In the first place specific directions are indispensable, since semimicro quantities are used; secondly, a general method described for one member of a particular group of compounds often requires radical alterations for different members of the same group. Let it be assumed, for example, that it is necessary to prepare a semicarbazone for the identification of a carbonyl compound. A general method could be described for the preparation of semicarbazones of aldehydes or ketones but it would be unsatisfactory, particularly in semimicro work. The lower carbonyl compounds do not form semicarbazones so easily as the higher members of the series; the time required for the formation of the semicarbazones varies from a few minutes to several weeks. Therefore, the course adopted has been to present the preparation of the semicarbazone of butanone and benzaldehyde, and to give directions after each preparation as to limitations and alterations of the method for other representative members of the series.

Most methods described in original papers on the preparation of derivatives for identification work are based on macroquantities, usually 1–5 g of the compound. The amount of the derivative yielded by macroquantities is so great that even a careless worker can perform 2–3 crystallizations and still have 100 mg of the derivative left. In the transition from macro- to semimicro quantities, the amounts of reagents are reduced tenfold or more and consequently conditions must be chosen that will insure: (a) completion of the reaction; (b) a minimum number of crystallizations to obtain a pure product; (c) exact quantities of solvent and conditions of crystallization; and (d) a sufficient yield of pure product for several melting-point determinations.

To meet some of these conditions the material in chapters 9–13 is arranged according to the following plan. For each major group or class of organic compounds, such as carbonyl compounds, amines, and the like, a section is first devoted to the general discussion of: (a) the reactions by which each type of derivative is prepared; (b) the limitations of each reaction; (c) side reactions and impurities that may separate along with the derivative; and (d) recommendations for the beginner as to the selection of the derivatives that should be tried first. This discussion is followed by a detailed description of the preparation of various derivatives of representative compounds of the series; in some cases, such as alcohols, eight to ten derivatives are described. For each type of recommended derivative, an attempt has been made to select a representative member from both the aliphatic and the aromatic series. The reactions by which derivatives are made should be considered as general reactions exhibited by all members of the group, but at varying rates. The speed may be so slow that the preparation of the derivative is impractical; since in any particular reaction of organic compounds there are several equilibria involved and hence several directions, some members of the group will not give the expected derivative. For example, treatment of formaldehyde with semicarbazide does not give a semicarbazone but a polycondensation product; further, some aldehydes and ketones in presence of sodium acetate used in the preparation of the derivative yield an acetylsemicarbazide and a hydrazodicarbonamide in addition to the semicarbazone.

In most cases, after the description of the preparation, brief notes are appended discussing the necessary changes in procedure for the preparation of the same type of derivative from other members of the same group or subgroup of compounds. Generally, there is a difference in reactivity between open-chain and cyclic derivatives, particularly between aliphatic and aromatic compounds. In some cases the aromatic

compounds react faster than the open-chain compounds, although no general guiding rule can be given. However, with reference to the solubility of derivatives, such a rule can be formulated. Derivatives of aromatic compounds are far less soluble in water and methanol (the pair of solvents most widely used in this work) than the same types of derivatives from open-chain compounds. Therefore, if a derivative is described for an open-chain compound with 4–6 carbon atoms, and it is desired to prepare the same type of derivative from a simple aromatic compound, the quantity of methanol used in the purification of the derivative should be increased. In most cases it is possible to start with about 50 mg or less of the aromatic compound, prepare a derivative, perform two or more crystallizations, and have 20–30 mg of the pure derivative left for determination of the melting point.

No matter how detailed a description of the procedure may be given, there is one variable that may cause difficulty for both the beginner and the advanced worker when semimicro or micro quantities are used, namely, the purity of the reagent used in the preparation of the derivative. The unknown substance is usually purified before it is subjected to a reaction for the preparation of derivatives. The purity of the reagent, however, is taken for granted, since it is guaranteed by the label of the manufacturer. This guarantee was made when the manufacturer bottled the compound. But 3,5-dinitrobenzoyl chloride and α-naphthyl isocyanate, two common reagents used in the derivatization of alcohols, slowly absorb moisture after the seal of the bottle is broken, even if the bottle is closed by a glass stopper. Thus, if one uses 100 mg of 3,5-dinitrobenzoyl chloride, he may be introducing a quantity of 3,5-dinitrobenzoic acid into the sample. This may be difficult to remove, since the procedure given was designated to remove only the very small quantity of 3,5-dinitrobenzoic acid that is bound to form, first, from the moisture in the vessel and alcohol, and second, from unreacted acid chloride.

Table VI shows the effect of the purity of reagents on the melting points of the derivatives. The 3,5-dinitrobenzoate melting at 93–95° requires at least 3 crystallizations from aqueous alcohol to raise the melting point to 104–105°. Since there is a loss of approximately 40–50 per cent in each crystallization, there will be only about 10 mg left, which must again be crystallized in order to obtain the correct melting point of the derivative—that is, 107–108°. On the other hand, from the sample melting at 102–103° after 2 crystallizations, about 20 mg of crystals remain, which melt at 107–108°.

Other than recommended derivatives. The table of derivatives listed on pages 358 to 458 includes other types of derivatives besides those

recommended. No attempt has been made to include all the derivatives that have been described in the literature for any particular compound. The selection was made after careful consideration of all the factors involved. In some cases the detailed preparation of other types of derivatives is given in the experimental part of this chapter. This indicates

TABLE VI

Effect of Purity of Reagent in Semimicro Preparation of Derivatives[5]

Reagent	Compound Derivatized	Yield of Derivative (mg)	Melting Point (°C)	
			Observed	*Accepted*
3,5-Dinitrobenzoyl chloride (A)[1]–100 mg	methanol (0.15 ml)	85	98–99	108
3,5-Dinitrobenzoyl chloride (B)[2]–100 mg	methanol (0.15 ml)	90	93–95	108
3,5-Dinitrobenzoyl chloride (C)[3]–100 mg	methanol (0.15 ml)	88	102–103	108
Semicarbazide hydrochloride (D)[4]–100 mg	butanone (200 mg)	130	135	135
Semicarbazide hydrochloride (E)[4]–100 mg	butanone (200 mg)	125	133	135
Semicarbazide hydrochloride (F)[4]–100 mg	butanone (200 mg)	132	132	135

[1] From original bottle with seal unbroken.
[2] From bottle standing on shelf for 10 months.
[3] Freshly purified by crystallization from dry carbon tetrachloride.
[4] Grades D, E, F represent three samples from different manufacturers: D was labeled "purified"; E was marked "regular"; and F was marked "highest purity."
[5] In each series the identical quantities and method were used; the derivative in each case was filtered, washed, and dried without further purification.

that such a derivative is useful for some particular members of the group of compounds under which it is described. It should be emphasized that if a derivative is not listed as being recommended, *this does not mean* that it is not useful for some or all members of the series. Therefore, if the recommended derivatives do not prove suitable, a selection should be made from the other derivatives listed. For this selection the literature should be consulted. References given in the bibliography at the end of each section in chapters 9–13 cover most of the derivatives listed in the tables. The first factor to be considered by a beginner in choosing derivatives other than those recommended is the availability of the reagent. If the reagent in question is not commercially available and not easily prepared, it is best, in most cases, to eliminate such a derivative from consideration.

When the derivative has been selected and the description of a method of preparing such a type of compound has been located in the literature, the problem for the beginner is how to apply the general method to a particular compound. The descriptions of methods found in the literature are of necessity condensed; since they are extremely general, they do not specify amounts of solvents and details of procedure. The experienced worker is able to glance at a general method and then adapt it to the particular compound at hand. The beginner, on the other hand, must gain such knowledge by experience. For these reasons it would be well to consider that the first attempt to prepare a derivative, by a general method described in the literature, will ***probably fail to yield satisfactory results.*** By considering the probable causes of failure and altering the conditions and procedure, it should be possible to adapt the general method to the particular synthesis under consideration.

Melting points of derivatives. The melting point of the derivative is the sole criterion in the final identification of the unknown. It is therefore necessary to discuss this topic at some length. The reader should review the section on melting points in Chapter 2, particularly pages 27–40.

The tables of the derivatives of compounds included in this text were compiled carefully after an examination of the literature. The following difficulties were encountered:

1. For many derivatives several melting points were listed; the values given may vary by only 1°–2°, or by as much as 10° or more. These variations in values are discussed on the next page.
2. In a few cases, particularly in recent literature, the melting points of derivatives given are stated to be corrected: that is, the correction for unequal heating of the thermometer has been applied. In most instances, however, there is no statement as to whether or not the correction has been applied. Obviously, however, many of the older values are uncorrected melting points; in such cases the compounds were not prepared primarily for identification purposes but in connection with some other type of investigation, and hence the correction of the melting point was not considered important. The correction for values of 100°–150° may amount to 1°–3°, but for values above 200° the correction may be as high as 4°–7°. Whenever a corrected melting point is given for a derivative in this text, **it is noted by an asterisk.**
3. In some cases the listing of two or more melting points is explained on the basis of the existence of two or more different crystalline modi-

fications;[1] for example, the 2,4-dinitrophenylhydrazone of acetaldehyde exists in the "stable" form, which melts at 168.5° (corrected), and the "metastable form," which melts at 157°. Under certain conditions an equilibrium mixture of the two forms is obtained that melts at 148°. However, most discrepancies in the melting points of organic compounds listed in the literature cannot be explained on the basis of the existence of more than one crystalline form. The usual assumption is that the various investigators used compounds of varying degrees of purity. Since the presence of impurities usually lowers the melting point of a compound, the rule followed by most workers in compiling data on melting points of organic compounds is to select the highest value from those listed. There is considerable evidence in the literature to justify such practice. For example, in checking the melting point of *d*-camphor semicarbazone, it was found that most modern standard works list it as 236° 238°; an older reference was found that gave the value of 245°. Investigation of the original literature disclosed that Tiemann,[2] who first prepared this derivative, gave as its melting point the value of 236°–238°. Rimini[3] pointed out that the true decomposition point is 245°. Finally Bredt and Perkin[4] prepared the compound by several different methods and found that it melts with decomposition at 247°-248° corrected. This value is 10° higher than the value listed in most modern works.

That such a situation is not always the case, however, is illustrated by the following two examples. The acetyl derivative of *p*-toluidine is a common derivative prepared for the identification of acetic acid, or acetic anhydride. The values listed in the literature are 147-8°,[5] 148–9°,[6] 151–152°,[7] 152°,[8] 153°,[9] 155.[10] Since this is a common derivative, it was prepared by one of the authors by the reaction of acetic anhydride and acetyl chloride with *p*-toluidine. After one crystallization the derivative gave a corrected melting point of 147°, and this did not change after six additional crystallizations. Therefore, the original listed value (on page 358) of this derivative of 155° was changed to 147°.

The other example concerns the melting point of piperonyl alcohol.

[1] For a brief discussion of anomalous melting point consult Skau and Wakeham in Weissberger, *Physical Methods of Organic Chemistry*, Vol. I, Interscience Publishers, Inc., New York, 1945, p. 27.
[2] Tiemann, *Ber.*, **28**, 2191 (1895).
[3] Rimini, *Gazette*, **30**, 603, (1900).
[4] Bredt and Perkin, *J. Chem. Soc.*, **103**, 2189 (1913).
[5] Matuura, *J. Sc., Hiroshima Univ., Ser. A*, **8**, 129 (1938) from *p*-toluidine and acetic anhydride in benzene; Kelbe, *Ber.*, **16**, 1200 (1883).
[6] Hugershoff, *Ber.*, **58**, 2484 (1925).
[7] Wedekind and Bruch, *Ann.*, **471**, 107 (1929).
[8] Curtius, *J. prakt. Chem.*, (2), **125**, 303 (1930).
[9] Gasopoulos, *Ber.*, *59*, 2187 (1926); Feitler, *Z. physik. Chem.*, **4**, 76 (1889).
[10] Frejka and Cizmar, *Chem. Listy*, **31**, 460 (1937).

This has been reported as 51°,[11] 52–53°,[12] 54°,[13] 57°,[14] and 58°.[15] Although in most cases the higher melting point was selected for listing, in this particular case 52–53° was selected, because the compound has been extensively investigated in the laboratory of one of the authors.

No satisfactory theoretical explanation can be offered for this behavior. The assumption that the correct melting point of aceto-*p*-toluidide is 147°, and that all the values reported by other investigators are erroneous because they probably used impure derivatives, is not plausible. This phenomenon, although not extremely common, is sufficiently recurrent to indicate that our knowledge concerning the melting points of solid organic compounds is incomplete. The phenomenon may be explained by the hypothesis that differences in the method of preparation of a compound and variations of the solvent, of the temperature, and of the concentration of the solution from which the compound is crystallized produce differences in crystal structure or crystal aggregation that account for the variation of the melting points. Such a hypothesis, however, requires a good deal of evidence for its substantiation, and such evidence as exists is extremely meager; hence the explanation must be regarded as speculative only.

4. It is not practical in a work of this type to list all the melting points that may be found in the literature for a particular derivative because in many cases more than two values are given that differ by several degrees; therefore, whenever *two or more values* have been found for the same derivative, a selection has been made in accordance with the following criteria: (a) preference has been given to values appearing in the recent literature; (b) preference has been given to values presented by investigators whose primary purpose was the determination of physical and related data for characterization work rather than to those appearing in papers dealing primarily with preparative work; (c) in general, whenever two values have been listed, the higher has been chosen. If the difference between the values of the melting point for the same derivative was 2° or less, no attempt was made to record the variation. If, however, the difference was 3° or more, *one other value* has been recorded in parenthesis under the selected value. In some instances a note appears at the end of the table regarding the difference, and it is recommended that the reader make use of these notes. Moreover, the listing of two

[11] Fittig and Remsen, *Ann.*, **159**, 138 (1871); Decker and Koch, *Ber.*, **38**, 1741 (1905); Mannich and Walther, *Arch. Pharm.*, **265**, 1 (1927)

[12] Berger, *J. Chem. Soc.*, **93**, 567 (1899); Carothers and Adams, *J. Am Chem. Soc.*, **46**, 1681 (1924).

[13] Vavon, *Compt. rend.*, **154**, 361 (1912); Braun and Wirz, *Ber.*, **60**, 102 (1927).

[14] Parijs, *Rec. trav. chim.*, **49**, 41 (1930).

[15] Orr, Robinson, and Williams, *J. Chem. Soc.*, **111**, 950 (1917).

values in the present work indicates that two or more values with differences of 3° or greater are to be found in the literature; a difference of 1–2° in the melting points of the same derivatives as given in standard works is the rule rather than the exception. It is highly recommended that one consult more complete listings of derivatives from the works given on pages 154–157.

Recommended practice for evaluation of melting-point determinations. The practical importance of the above discussion becomes apparent when one prepares one or two derivatives for the final identification of a probable compound and finds that they differ by 2–3° from the value listed in the literature; yet the derivatives prepared do not show much alteration in the melting point on two successive crystallizations. The following practice is recommended for beginners:[16] *Prepare one or better two different derivatives of the probable compound. From each derivative save a few milligrams and recrystallize the rest. If the difference between the first and second lots of crystals is not more than 1–2°, check the melting point of the same derivative of the probable compound as listed in the tables. If the difference is not more than 2–3°, prepare the same derivative from a pure sample of the compound tentatively identified as the unknown, using the same quantities of reagents, procedures, and crystallizations as those used in the preparation of the derivative of the unknown. Mix a few milligrams of each of the two derivatives obtained from the unknown and from the pure sample of the compound tentatively identified as the unknown. If the mixture does not show a variation of more than 1° from the melting point of either component alone, the proof of identity may be considered conclusive. It is recommended that beginners prepare two different derivatives; only after considerable experience has been gained should the conclusive identification be based on the preparation of one derivative and a mixed melting point.*[17]

An explanation for the above practice may be in order at this point. When semimicro quantities are used, the amount of derivative available after 1–2 crystallizations is usually 50–100 mg if one begins with 100–200 mg of the unknown; but in some cases it may require a total of 4–5 crystallizations to obtain a derivative that has the melting point shown in the literature. In other cases, for reasons pointed out above, *the melting point given in the literature will not be obtained, no matter how many recrystallizations are performed.* Therefore, if all other evidence from solubility data, functional-group tests, and physical constants fit a par-

[16] In college and university laboratories when "student unknowns" are being identified this practice is to be modified in accordance with directions by the instructor

[17] The reservations given under the discussion of mixed melting points (p 39) should be reviewed.

ticular probable compound, the procedure outlined in the above recommended practice with reference to derivatives is regarded as sound.

Suggestions for preparation of derivatives. Unless the beginner is familiar with the semimicro procedures and techniques used in crystallization and filtration, it is recommended that he read thoroughly pages 11–27 and gain some practice by preparing one or two derivatives listed in this chapter. The yields specified after each preparation are in most cases those obtained by persons who had had a year or less of experience in an organic laboratory. It is also suggested that the beginner review the reactions in Chapter 8 by which the derivative is prepared. The rule given in the preceding section with reference to the number of crystallizations and melting-point determinations has been found very useful.

In general, derivatives melting in the range of 50° and below should not be selected, for reasons pointed out on page 195. There are occasions, however, when such derivatives are the only ones available. For the determination of the melting points of derivatives, which melt at the range of 50° or below, and in general of all crystalline compounds that cannot be pulverized into a fine powder, the method given in Chapter 2 is recommended. About 1–2 mg of the substance are cautiously placed on a watchglass and passed over a small flame of the microburner until it melts. The capillary is then filled and the melting point determined as directed on pages 37–9. For the purification of such derivatives, microfractional vacuum distillation may be used as directed on page 62.

Derivatives of Carboxylic Acids

The most important derivatives for the identification of carboxylic acids and their salts are *amides*, *substituted amides*, and *esters*, as shown by the following equations:

$$CH_3(CH_2)_4COOH \xrightarrow{SOCl_2} \underset{n\text{-Caproyl chloride}}{CH_3(CH_2)_4COCl} + 2\ NH_3 \longrightarrow \underset{n\text{-Capramide}}{CH_3(CH_2)_4CONH_2} + NH_4Cl \qquad (1)$$

$$CH_3(CH_2)_2COOH \xrightarrow{SOCl_2} CH_3(CH_2)_2COCl + \underset{\text{Aniline}}{2\ C_6H_5NH_2} \longrightarrow \underset{\substack{n\text{-Butyranilide}\\ \text{(N-Phenyl-}n\text{-butyramide)}}}{CH_3(CH_2)_2CONHC_6H_5} + C_6H_5\overset{+}{N}H_2H\overset{-}{Cl} \qquad (2)$$

or

$$+2\ BrC_6H_4NH_2 \longrightarrow \underset{\substack{n\text{-Butyryl-}p\text{-bromoanilide}\\ \text{(N-}p\text{-Bromophenyl-}n\text{-butyramide)}}}{CH_3(CH_2)_2CONHC_6H_4Br} + BrC_6H_4\overset{+}{N}H_2H\overset{-}{Cl}$$

$$CH_3CH_2COOH + CH_3C_6H_4NH_2 \xrightarrow{180°} CH_3CH_2CONHC_6H_4CH_3 + H_2O \quad (3)$$

p-Toluidine — Propionyl-*p*-toluidide (N-*p*-Tolylpropionamide)

$$2\,CH_3COOH + CH_2(C_6H_4NH_2)_2 \longrightarrow CH_2(C_6H_4NHCOCH_3)_2 + 2\,H_2O \quad (4)$$

4,4'-Diaminodiphenylmethane — 4,4'-Methylenebisacetanilide

$$CH_3COONa + O_2NC_6H_4CH_2Cl \longrightarrow CH_3COOCH_2C_6H_4NO_2 + NaCl \quad (5)$$

p-Nitrobenzyl chloride — *p*-Nitrobenzyl acetate

or

$$+ C_6H_5COCH_2Cl \longrightarrow CH_3COOCH_2COC_6H_5 + NaCl$$

Phenacyl chloride — Phenacyl acetate

or

$$+ BrC_6H_4COCH_2Br \longrightarrow CH_3COOCH_2COC_6H_4Br + NaBr$$

p-Bromophenacyl bromide — *p*-Bromophenacyl acetate

$$CH_3COOH + C_6H_5NHNH_2 \longrightarrow C_6H_5NHN\overset{+}{H_3}[\overset{-}{O}COCH_3] \quad (6)$$

Phenylhydrazine — Phenylhydrazonium acetate

or

$$+ C_6H_5CH_2NH_2 \longrightarrow C_6H_5CH_2N\overset{+}{H_3}[\overset{-}{O}COCH_3]$$

Benzylamine — Benzylammonium acetate

$$CH_3COOH + C_6H_4(NH_2)_2 \longrightarrow C_6H_4{<}^{NH}_{N}{>}CCH_3 + 2\,H_2O \quad (7)$$

o-Phenylenediamine — 2-Methylbenzimidazole

$$C_6H_5CH_2SC(NH_2)_2\overset{+\,-}{Cl} + CH_3COONa \longrightarrow C_6H_5CH_2SC(NH_2)_2\overset{+\,-}{[OCOCH_3]} + NaCl \quad (8)$$

S-benzylthiuronium chloride — S-benzylthiuronium acetate

Inspection of equations (1)-(4), inclusive, shows that these derivatives are amides and substituted amides. The preparation of aliphatic amides (equation 1) is not recommended for semimicro quantities. The amides are usually obtained by first preparing the acid chloride and treating the latter with an excess of aqueous ammonia at low temperatures. One difficulty arises from the fact that the acid chloride undergoes hydrolysis and ammonolysis at the same time, thus reducing considerably the yield of the amide. If the temperature is kept low and the acid halide is not very reactive, as in the case of the higher fatty acids and aromatic compounds, the degree of hydrolysis is kept at a minimum. Another difficulty arises from the significant solubilities of amides in alcohol-water mixtures, which render it difficult to crystallize

100–200 mg of an amide several times and leave a sufficient amount of the pure derivative for a melting-point determination.

Of the substituted amides the *p-toluidides* are recommended. They are easily prepared and have desirable crystallizing properties. If the carboxylic acid contains less than 8 carbon atoms, the *p*-toluidide may be conveniently prepared by heating the acid with an excess of *p*-toluidine at 180°–200°. The reaction mixture is extracted with dilute hydrochloric acid to remove the excess of the base, and with dilute sodium hydroxide to remove traces of unreacted acid, and is then crystallized from an alcohol-water mixture. The toluidides of the higher fatty acids and of the aromatic carboxylic acids are prepared by first converting the acid to the acid chloride and then adding an excess of *p*-toluidine. The same method is used for the preparation of anilides and *p*-bromoanilides. For the higher fatty acids the derivatives obtained with 4,4′-diaminodiphenylmethane are recommended. The anilides are prepared by methods similar to those employed for *p*-toluidides and may be used if *p*-toluidine is not available.

Equation (5) shows the preparation of *p-nitrobenzyl* and *phenacyl esters* of carboxylic acids that may be used for characterization. In addition to the *p-nitrobenzyl*, *phenacyl*, and *p-bromophenacyl*, the *p-chlorophenacyl* and *p-phenylphenacyl* esters may be prepared by similar reactions. A great amount of caution, however, should be exercised in the use of these reactions by the beginner. All of the phenacyl halides have lachrymatory properties and further cause blisters on contact with the skin. Handling of the crystalline esters may cause an irritation between the fingers, probably due to the small amounts of halide adhering to the crystals of the esters.

On the other hand, the preparation of the *p*-nitrobenzyl and of the phenacyl esters as derivatives is very valuable when the acids cannot be easily separated from aqueous solutions as is often the case in the hydrolysis of the esters of lower carboxylic acids. For the preparation of the *p*-nitrobenzyl and phenacyl esters, the carboxylic acid is converted to the sodium salt by neutralization with dilute sodium hydroxide or sodium carbonate and is then heated for an hour or more with an alcoholic solution of the halide. It is essential to avoid the use of an excess of the halide, since it cannot be easily removed from the ester. The esters are recrystallized from alcohol; their separation from solution is rather slow and sufficient time should be allowed for the oils that often separate to change into the crystalline state.

Equation (6) represents the preparation of salts of carboxylic acids with various organic bases that may be used for characterization. In

addition to ***phenylhydrazine*** and ***benzylamine;*** other bases reported in the literature for the same purpose are ***phenylethylamine*** and ***piperidine.*** Although phenylhydrazine is a common reagent and the preparation of the salt appears relatively simple, the preparation of this type of derivatives is not recommended for semimicro quantities except with acids that are not easily soluble in water. The phenylhydrazine salts should be purified immediately after preparation and dried as rapidly as possible, since they change slowly when exposed to air. The use of benzylamine with heating gives *N-benzylamides;* the original article cited in the Bibliography Section should be consulted for details and the melting points of the N-benzylamides.

Equation (7) represents the formation of a *2-alkylbenzimidazole* by the reaction of the carboxylic acid with *o*-phenylenediamine. Equal amounts of the amine and the carboxylic acid are refluxed with a small amount of dilute hydrochloric acid for 15–20 minutes; after the solution is cooled, aqueous ammonia is added until the alkylbenzimidazole separates out. The derivative is crystallized from alcohol or converted to the picrate by dissolving it in the minimum amount of alcohol and adding the solution to a saturated alcoholic solution of picric acid.

Equation (8) represents the formation of *S-benzylthiouronium derivative* of a carboxylic acid. The reagent, *S*-benzylthiouronium chloride (see page 324), prepared by heating thiourea with benzyl chloride, forms the crystalline derivative easily on mixing with a solution of the alkaline salt of the organic acid. The resulting thiouronium salts should be recrystallized from anhydrous solvents (alcohol, dioxane) to avoid hydrolysis. The following examples illustrate the details of the preparation of several derivatives.

9.1 Propiono-p-toluidide. Place in an 8-inch test tube 0.3 ml of propionic acid and 1.2 g of *p*-toluidine. Immerse the tube in an oil bath and raise the temperature slowly over a period of 10 minutes to 190°. Keep the temperature at 190°–200° for 30 minutes; then remove the tube and allow to cool. Add 7 ml of 5 per cent hydrochloric acid and wash down the inner sides of the tube, by means of a pipette dropper, with 1 ml of methanol. Heat nearly to boiling and set in cold running water to cool for 10–15 minutes, shaking the tube from time to time. Filter; wash the solid with a mixture of 2 ml of 5 per cent hydrochloric acid and 3 ml of water, then with 5 ml of water, followed by 5 ml of 2 per cent sodium hydroxide solution, and finally twice with 3 ml of water. By means of the spatula remove the solid, together with filter paper, and place in an 8-inch test tube. Add 3 ml of methanol and heat nearly to boiling until the crystals are completely dissolved. Add as much char-

coal as can be placed on one half of the spatula blade and heat for a few seconds; then set aside. Place the perforated porcelain disc inside the funnel; set the filter paper on top of the porcelain disc and wet it with 3–4 drops of water. Fit the funnel into an 8-inch tube with side-arm and start light suction. Inspect the filter paper and see that it fits tightly on the sides of the funnel. Add to the filter funnel 4–5 drops of methanol and then drain the receiving tube. Heat the solution of the derivative to boiling and pour slowly into the filter. The filtrate should be clear. If a minute amount of charcoal has passed through it, it may be overlooked, since the compound is to be recrystallized. About 1 ml of methanol is poured dropwise down the sides of the tube that was used to prepare the solution and, after rotating and heating for a few seconds, the washings are added into the filter. The suction is discontinued and 1.5–2 ml of water are added by means of the pipette dropper to the filtrate. The tube is heated until the cloudiness disappears and is then cooled for 15–20 minutes. The crystals are filtered and washed 3 times with 3–4 ml of water. The yield of dry crystals is 75–100 mg; the melting point is 122–123°. In practice, the crystals are recrystallized immediately after filtration from 3 ml of methanol and 1.5 ml of water, using the procedure described. The yield of pure propiono-*p*-toluidide is 50–70 mg, melting at 123°–124°.

Note: The preparation of the *p*-toluidide is described in great detail for the beginner who is not acquainted with semimicro techniques.

The solubility of *p*-toluidides decreases with an increase of the molecular weight of the acid. Thus, by using 0.3 ml of *n*-caproic acid with the procedure described, and the same number of crystallizations, about 110–130 mg of *n*-caproyl-*p*-toluidide are obtained, melting at 74°–75°. However, as the molecular weight increases, there is a tendency for the *p*-toluidides to separate as oils. The *p*-toluidide of *n*-caprylic acid illustrates this tendency. On heating, with dilute hydrochloric acid, the reaction mixture of 0.3 ml of acid and 1.2 g of *p*-toluidine, an oil separates that does not crystallize on cooling. If, during cooling, the tube is shaken frequently and the inner sides of the tube are scratched with a glass rod, the oil crystallizes into a dark mass. After washing as described, it is dissolved in 5 ml of hot ethanol, treated with charcoal, and filtered; the filtrate is then diluted with 2 ml of water. The crystals that separate on cooling are crystallized again from 5 ml of ethanol and 3 ml of water. The yield is about 200–220 mg of *n*-capro-*p*-toluidide, melting at 70°.

The preparation of the derivatives of fatty acids having 5–8 carbon atoms may be accomplished by using 0.1–0.2 ml of the sample. The dry sodium salt of the carboxylic acid may be used instead of the free acid. In such cases an equal amount of sodium salt and concentrated hydrochloric acid is placed in the tube. The toluidine is added and the mixture is heated gradually until a

temperature of 140° is reached; it is kept at this temperature for 15 minutes. The temperature is then raised to 190–200° and maintained for 30 minutes. This method is effective when aqueous solutions of the lower carboxylic acids are involved. Since it is difficult to extract small amounts, it is more appropriate to neutralize the solution carefully with sodium carbonate and evaporate the salt solution to dryness, using this salt mixture for the preparation of the derivative.

9.2 Adipobis-p-toluidide. The procedure described in Section 9.1 (page 208) is followed, using 200 mg of adipic acid and 1 g of *p*-toluidine. Add to the cooled reaction mixture 7 ml of 5 per cent hydrochloric acid and heat nearly to boiling. Cool slightly and pour the contents of the tube into a mortar. Grind the mass of crystals until no lumps remain. Replace the mixture in the 8-inch tube and heat. Filter and wash as described under 9.1. Dissolve in 15 ml of ethanol and, after treating with charcoal, filter. Add 1 ml of water and cool. The solid that separates is crystallized after filtration from 12–15 ml of ethanol. About 150 mg of the pure crystals, melting at 239°, are obtained.

Note: Dicarboxylic acids may react with only one mole of the base to give the mono-*p*-toluidide. This tendency is particularly manifested when the dicarboxylic acid forms an anhydride upon heating. For example, phthalic and maleic acids give the mono-*p*-toluidide when they are heated with *p*-toluidine.

9.3 Benzo-p-toluidide. Place in an 8-inch distilling tube arranged as shown in Figure 62, page 178, 200 mg of benzoic acid. Lift the cork holding the microcondenser and add, by means of the pipette dropper, 0.6–0.8 ml of thionyl chloride. Heat in a water bath at 75°–85° for 30 minutes. Lift the cork and add a solution of 1 g of *p*-toluidine in 25 ml of dry benzene. (**Caution:** *Flames should not be in the vicinity.*)

Replace microcondenser and reflux gently for 15 minutes. Cool, add 5 ml of water, and transfer the mixture into a small separatory funnel or into an 8-inch tube provided with separatory stopper. Wash distilling tube with 1 ml of ethanol and add to the mixture in the separatory vessel. Shake benzene-water mixture gently to insure thorough mixing but to avoid formation of an emulsion. Remove the aqueous layer and wash the benzene solution successively with 5 ml of 5 per cent hydrochloric acid, 5 ml of 5 per cent sodium hydroxide, and 5 ml of water. Allow sufficient time after shaking for complete separation of the two immiscible layers. Pour the benzene solution into an evaporating dish and evaporate cautiously over a water bath. Wash separatory vessel with 1–2 ml of ethanol and add the washings to the evaporating dish. Add to the residue 5 ml of ethanol and warm until it is completely dissolved. Add

charcoal and filter by suction. Wash the dish, by means of the pipette dropper, with 1–2 ml of ethanol and pour the washings through the filter. Add 2–3 ml of water slowly to the filtrate and heat tube until the cloudiness disappears. Cool and filter the crystals; wash crystals twice with 3 ml of water, and dissolve directly in 5 ml of hot ethanol. Filter and add 2 ml of water. Cool and filter the toluidide. About 200 mg of pure benzo-*p*-toluidide, melting at 157–158°, are obtained.

Note: This method illustrates the preparation of *p-toluidides, anilides, p-bromoanilides*, and other substituted amides by reaction of the amine with the acid chloride. For the preparation of the acid chloride, 50–100 mg of the carboxylic acid may be used, and proportionate amounts of the other reagents.

9.4 n-Butyranilide. Place in an 8-inch tube 200 mg of butyric acid and use the procedure as described in Section 9.3, except that a solution of 1.5 ml of aniline is substituted for *p*-toluidine. The residue, after evaporation of benzene, is dissolved into 4 ml of methanol and 2 ml of water. The crystals that separate after the first crystallization are dissolved in 5 ml of hot methanol and filtered; to the hot filtered solution 4 ml of water are added. The yield of pure *n*-butyranilide, melting at 94–95° is about 80–90 mg.

Note: The solubility of the anilides of aryl carboxylic acids is much less than those of the aliphatic; hence the same variation in the amount of alcohol and water for crystallization is observed as in the *p*-toluidides. For the preparation of *p*-bromoanilides, the same procedure is followed as for the preparation of benzoyl-*p*-toluidide (9.3). The preparation of *p*-bromoanilides of the lower carboxylic acids is preferred over the anilides if the quantities of the carboxylic acid available are small.

As stated on page 209, the sodium salt of the carboxylic acid may be used instead of the free acid for the preparation of the substituted amides. In cases where it is required to prepare the acid chloride and then react it with the arylamine, the dry salt is treated with the thionyl chloride as described under the preparation of benzo-*p*-toluidide (9.3), using the same quantities of salt instead of the acid. Dicarboxylic acids, such as succinic, glutaric, and maleic, which form anhydrides easily, are likely to give the anhydride rather than the acid chloride by reaction of the salt with thionyl chloride; in such cases the resulting anhydride may form the monosubstituted amide instead of the diamide. For example, maleic acid may yield under such conditions the mono-*p*-toluidide instead of the di-*p*-toluidide. On the other hand, aromatic acids that contain a negative substituent in the position para to the carboxyl group (*p*-chlorobenzoic, *p*-bromobenzoic, *p*-hydroxybenzoic, and the like), do not react easily with thionyl chloride. In such cases it is often possible to convert the carboxylic acid to the acid chloride by the use of phosphorus pentachloride.

9.5 4, 4'-Methylenebisstearanilide. Place in an 8-inch test tube 80 mg of 4, 4'-diaminodiphenylmethane and 250 mg of stearic acid. Clamp the tube to a stand and heat, by means of a microburner, for about 5 minutes. The temperature within the tube should be such that the water vapor formed rises to the mouth of the tube. Cool and add 5 ml of water and 2 ml of ethanol. Heat to boiling and add a drop of phenolphthalein and, by means of a pipette dropper, sufficient 5 per cent sodium hydroxide to render the solution alkaline. Filter and wash the crude diamide twice with 4–5 ml of water. Transfer the crystals into a test tube and add 4 ml of methanol and 5 ml of benzene. Heat, filter, and cool the solution; after cooling for 15 minutes, filter and dry the crystals.

9.6 Cinnamamide. Prepare the acid chloride from 0.2 g of cinnamic acid and 0.8 ml of thionyl chloride as described in Section 9.3. Remove distilling tube and cool in an ice-water mixture (hood). Add 5 ml of ice-cold concentrated aqueous ammonia. Stir by means of a glass rod and allow the tube to stand for 5 minutes in the cold, shaking from time to time. Filter the crude amide and dissolve in 3 ml of alcohol, filter, and add 2 ml of water. The yield is 70 mg, melting at 147°–148°.

Note: For the ammonolysis of very reactive halides, consult Section 8.38, page 187.

9.7 p-Nitrobenzyl salicylate. Place in an 8-inch test tube 250 mg of salicylic acid and then add a drop of phenolphthalein and 2–3 drops of 5 per cent sodium carbonate. Warm the tube over a free flame and continue the addition of carbonate dropwise until the acid has been neutralized and the color of the solution is just pink. Warm the solution in order to be certain that all the acid has reacted. Add 2 drops of 5 per cent hydrochloric acid so that the pink color of the solution is discharged. Add 200 mg of *p*-nitrobenzyl chloride or *p*-nitrobenzyl bromide, 8 ml of alcohol, and a small boiling stone. (**Caution:** Be careful in handling the *p*-nitrobenzyl halides. Replace the stopper of the bottle immediately and avoid contact with the skin.) Arrange tube for reflux (page 15) and boil gently for 1.5 hours. Cool and add 1 ml of water and scratch the sides of the tube. After 20 minutes filter the ester and wash first with 4 ml of 5 per cent sodium carbonate and then twice with 4 ml of water. Dissolve crystals in 8–10 ml of hot alcohol, filter, and add water to filtrate dropwise until a cloudiness appears. Heat tube until cloudiness disappears and then cool, scratching the sides of the tube with a glass rod. Cool for 15 minutes; then filter crystals. Wash with 1–2 ml 50 per cent methanol and dry on paper disc. Avoid handling or contact

of the crystals with the skin. The yield is 110 mg; the melting point, 97–98°.

Note: Consult section on esterification (8.30), page 182, for further discussion of the reaction. The formation of *p*-nitrobenzyl and substituted phenacyl esters is slow and refluxing of semimicroquantities should be continued for 1.5–2 hours or more to insure complete reaction. For example, by using *p*-nitrobenzyl chloride the same method and quantities as outlined above and refluxing for one hour, the following results were obtained (in each case the temperature listed after the name of the acid is the melting point of the *p*-nitrobenzyl ester after one crystallization; the temperature in the parentheses is the melting point listed in the literature): acetic, 72° (78°); succinic, 71° (88°); citric, 74° (102°); benzoic, 65° (99.5°). Since pure *p*-nitrobenzyl chloride melts at 71°, it is evident that after one hour the reaction was only partially completed. For these reasons the preparation of *p*-nitrobenzyl and substituted phenacyl esters is to be undertaken only if other derivatives are not suitable. The general procedure for the preparation of the phenacyl or substituted phenacyl esters is to neutralize 1 milliequivalent of the carboxylic acid with 5 per cent sodium carbonate as outlined above and then add 1 milliequivalent of the phenacyl or substituted phenacyl halide and 5–8 ml of alcohol and proceed as outlined in Section 9.7.

The procedure for determining the *neutral equivalent* of an acid is given in the Appendix (page 469).

Note: Bibliography appears after the following discussion of acid halides and anhydrides (page 215).

Derivatives of Acid Halides and Anhydrides

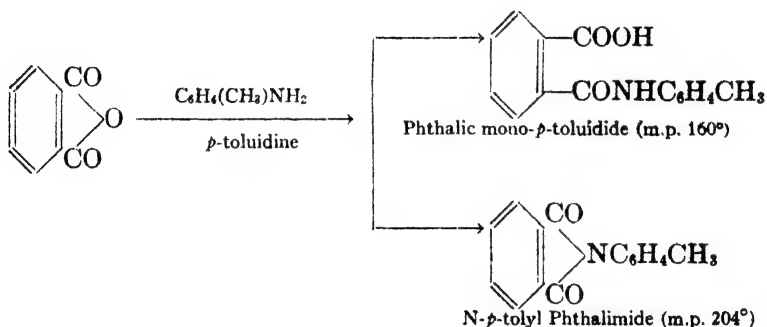
Acid halides. The reader should review the discussion of carboxylic acids if the substance under investigation has been tentatively identified as an acid halide or anhydride. It is evident that, since the acid is usually converted to the acid chloride for the preparation of amides, anilides, *p*-bromoanilides and toluidides, these same derivatives may be used to advantage for the characterization of acid halides. About 100–200 mg or less of the acyl halide are dissolved in 10 ml of dry benzene and 500 mg of the arylamine (aniline, *p*-toluidine, *p*-bromoaniline) are added; the mixture is refluxed for 10 minutes and then treated as described under Procedure 9.3, page 210.

Acid chlorides react with alcohols or phenols to form esters. If the ester is solid, it may be used as a useful derivative for identification (see page 218). The hydrolysis of the chloride gives an acid that, if solid and slightly soluble in water, may be used for identification. In such cases 100–200 mg of acid chloride are boiled with 5 ml of 5 per cent sodium car-

bonate solution for 20 minutes. If the acyl halide is reactive, the refluxing may be shortened to a few minutes. The solution is cooled, extracted with 5 ml of ether, and the aqueous layer is separated and acidified with dilute sulfuric acid to liberate the carboxylic acid.

The selection of the appropriate derivative for acyl halides should be based on the solubility and the melting point of the derivative. For example, assume that tests of the compound under investigation indicate that it is a nitrobenzoyl chloride. The anilides and *p*-toluidides of the nitrobenzoic acids melt above 200°, whereas their esters with the lower alcohols melt between 70–150°; in this case it will be more appropriate to react the acid chloride with methanol and prepare the ester as directed on page 221, rather than to prepare any of the substituted amides.

Acid anhydrides. The discussion and reactions given for the acyl halides apply with few modifications to the acid anhydrides. The anhydrides most commonly encountered are: acetic, succinic, maleic, and phthalic. Hydrolysis of the anhydrides yields acids; reaction with amines yields amides or substituted amides. Anhydrides of dibasic acids, on reacting with arylamines, may give the monoamide or the imide:

$$C_6H_4(CO)_2O \xrightarrow[p\text{-toluidine}]{C_6H_4(CH_3)NH_2} \begin{cases} C_6H_4(COOH)(CONHC_6H_4CH_3) & \text{Phthalic mono-}p\text{-toluidide (m.p. 160°)} \\ C_6H_4(CO)_2NC_6H_4CH_3 & \text{N-}p\text{-tolyl Phthalimide (m.p. 204°)} \end{cases}$$

In reacting with alcohols, the anhydrides of dibasic acids yield the acid esters; thus phthalic anhydride and 3-nitrophthalic anhydride yield, with alcohols, sparingly soluble acid esters that may be used as derivatives (see page 219).

9.8 Aceto-p-toluidide. Place in a test tube 100 mg of acetic anhydride and 50 mg of *p*-toluidine. Arrange tube with reflux condenser and heat over a very small flame for 10 minutes so that the mixture just boils; when the mixture has cooled, add 2 ml of methanol and heat until the solid has disintegrated. Add 6 ml of water and filter the crude toluidide. Wash with water and recrystallize from 50 per cent methanol. The yield is 40–50 mg, melting at 147°.

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Preparation of Derivatives—Continued

Derivatives of Alcohols and Phenols

THE reactions employed to prepare derivatives for the identification of hydroxy compounds are illustrated in the following equations:

$$NO_2 \cdot C_6H_4COCl + CH_3OH \rightarrow NO_2 \cdot C_6H_4COOCH_3 + HCl \quad (1)$$
p-Nitrobenzoyl chloride — Methyl *p*-nitrobenzoate

$$(NO_2)_2C_6H_3COCl + C_2H_5OH \rightarrow (NO_2)_2C_6H_3COOC_2H_5 + HCl \quad (2)$$
3, 5-Dinitrobenzoyl chloride — Ethyl 3, 5-dinitrobenzoate

$$NO_2C_6H_3(CO)_2O + CH_3OH \rightarrow NO_2C_6H_3(COOH)COOCH_3 \quad (3)$$
3-Nitrophthalic anhydride — Methyl 3-nitrophthalate

$$C_{10}H_7NCO + C_3H_7OH \rightarrow C_{10}H_7NHCOOC_3H_7 \quad (4)$$
α-Naphthyl isocyanate — *n*-Propyl-α-naphthylurethan*

$$NO_2C_6H_4NHCOCl \rightarrow NO_2C_6H_4NCO + HCl \quad (5)$$
p Nitrophenylcarbamyl chloride — *p*-Nitrophenyl isocyanate

$$NO_2C_6H_4NCO + CH_3OH \rightarrow NO_2C_6H_4NHCOOCH_3 \quad (6)$$
Methyl-*p*-nitrophenylurethan*

$$BrC_6H_4CON_3 \rightarrow BrC_6H_4NCO + N_2$$
p-Bromobenzazide — *p*-Bromophenylisocyanate

$$BrC_6H_4NCO + C_2H_5OH \rightarrow BrC_6H_4NHCOOC_2H_5 \quad (7)$$
Ethyl-*p*-bromophenylurethan*

$$C_{10}H_7NCO + C_6H_5OH \rightarrow C_{10}H_7NHCOOC_6H_5 \quad (8)$$
Phenyl-α-naphthylurethan*

$$C_6H_5ONa + ClCH_2COOH \rightarrow C_6H_5OCH_2COOH + NaCl \quad (9)$$
Chloroacetic acid — Phenoxyacetic acid

$$C_6H_5OH + 3\ Br_2 \rightarrow C_6H_2Br_3OH + 3\ HBr \quad (10)$$
2, 4, 6-Tribromophenol (Picric Acid)

$$C_6H_5OH + 3\ HNO_3 \rightarrow C_6H_2(NO_2)_3OH + 3\ H_2O \quad (11)$$
2, 4, 6-Trinitrophenol

$$ArONa + ClC_6H_3(NO_2)_2 \rightarrow ArOC_6H_3(NO_2)_2 + NaCl \quad (12)$$
2, 4-Dinitrochlorobenzene — 2, 4-Dinitrophenyl ether

Equations (1), (2), and (3) represent the formation of sparingly soluble aromatic esters. The *3,5-dinitrobenzoates* are recommended for

* Urethans are also called *carbamates* as esters (NH_2COOR) of carbamic acid; thus $C_6H_5NHCOOC_2H_5$ may be called ethyl-N-phenylcarbamate. However, phenylcarbamates may be regarded as derivatives of *carbanilic acid*, $C_6H_5NHCOOH$, and therefore called *carbanilates*. Unfortunately, all three systems of nomenclature are in present use. Similarly, α-naphthylurethans in the more recent nomenclature are called 1-naphthalenecarbamates.

most primary and secondary alcohols. The *3-nitrophthalates* are useful for the derivatization of glycols and some of their hydroxyethers.

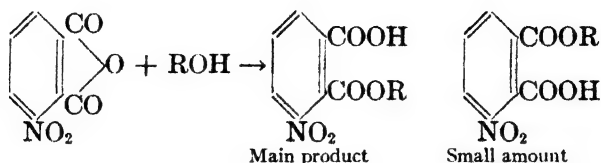
In the preparation of 3,5-dinitrobenzoates, the alcohol is heated for several minutes with 3,5-dinitrobenzoyl chloride. The amount of alcohol used should be in excess. so as to convert the acid chloride as completely as possible to the ester. Addition of water at the end of the heating period causes the separation of the solid esters. A small amount of 3,5-dinitrobenzoic acid and acid anhydride usually separate with the ester from the hydrolysis of the acid chloride. Hydrolysis occurs during heating as a result of reaction with moisture derived from the alcohol or the walls of the vessel, and also at the end of the reaction from the unreacted acid chloride. In order to remove the small amount of dinitrobenzoic acid, the solid ester is vigorously shaken with a solution of sodium carbonate and then recrystallized. When the amount of hydroxy compound is less than 100 mg, it is advisable to heat it with 3,5-dinitrobenzoyl chloride in presence of an inert solvent, such as isopropyl ether, dry benzene, or pyridine, as described on page 222. In general, this method should be used whenever the formation of the ester is slow, as in the case of tertiary alcohols. For example, when 30 mg each of *n*-butyl, isobutyl, *sec*-butyl, and *tert*-butyl alcohols and 50 mg of 3,5-dinitrobenzoyl chloride were heated for 30 minutes, the yields of the dinitrobenzoates in milligrams were, respectively, 16, 20, 18, and 0.5. It is obvious that the yield of the ester from the tertiary alcohol is insufficient for the ordinary methods of purification and melting-point determination. In such cases it is advisable to boil the alcohol for an hour or two with the dinitrobenzoyl chloride and pyridine dissolved in isopropyl ether (page 222). In the absence of a proton acceptor there is a tendency for tertiary alcohols to form the halide, RX, beside an olefin.

The 3,5-dinitrobenzoates form crystalline complexes with aromatic amines. The complexes with α-naphthylamine are particularly useful because they have characteristic colors from orange to red according to the radical attached to the hydroxyl group. Further, they form well-defined crystals, having definite melting points and may be used to purify those 3,5-dinitrobenzoates that are not easily crystallized.

Although the presence of water is of disadvantage in the preparation of 3,5-dinitrobenzoates, it is possible to prepare these derivatives from dilute aqueous solutions of the alcohols. The acid chloride is dissolved in purified ligroin and then is shaken with a 5 per cent aqueous solution of the alcohol in presence of sodium acetate. It is possible by this method to prepare derivatives from 500 mg of alcohol when it is admixed with 10 ml of water.

The reaction of 3-nitrophthalic anhydride with alcohols gives chiefly 2-monoalkyl esters of 3-nitrophthalic acid and only small quantities of the 1-monoalkyl isomeric esters.

$$\text{(CO)}_2\text{O}\ (\text{ring, } NO_2) + ROH \rightarrow \text{COOH, COOR}\ (\text{ring, } NO_2) \qquad \text{COOR, COOH}\ (\text{ring, } NO_2)$$

Main product — Small amount

The reaction with the lower alcohols takes place readily if the mixture of 3-nitrophthalic anhydride and alcohol is heated in a water bath until a homogeneous melt is obtained. For higher alcohols, the mixture is dissolved in dry toluene and refluxed. One disadvantage of the 3-nitrophthalates for semimicro work is their tendency to separate as oils, which renders their separation from the reaction mixture and subsequent crystallization difficult and tedious. Nevertheless, their use is advisable whenever the 3,5-dinitrobenzoates and urethans are not suitable.

Equation (4) represents the formation of a *urethan* or *carbamate*. The simplest method is to react the alcohol with an isocyanate, RNCO; a substituted carbamyl chloride or an azide may be used in place of the isocyanate, since both of these yield the isocyanate readily, as shown in Equations (5) and (7). The recommended reagent, however, is α-naphthyl isocyanate. The mixture of hydroxy compound and isocyanate is warmed in a perfectly dry tube or dissolved in petroleum ether (also called ligroin) and refluxed. Along with the urethans, a certain amount of substituted ureas is almost always formed by the reaction of the isocyanate with water present in the alcohol or moisture in the reaction vessel.

Although it is desirable that every trace of moisture be excluded, this result is difficult to achieve in actual practice. The reaction, however, is restricted to such hydroxy compounds as may be rendered anhydrous. The reaction mixture containing the urethan and some of the substituted urea is extracted with hot petroleum ether, which dissolves the urethan but not the urea. In most cases the urethan crystallizes on cooling if the sides of the glass tube are rubbed with a rod, but in some cases crystallization is slow.

The preparation of other substituted urethans has been proposed in the literature; the following represents only a partial list: *phenyl*, *β-naphthyl*, *o-nitrophenyl*, *p-nitrophenyl*, *m-nitrophenyl*, *3,5-dinitrophenyl*, *p-bromophenyl*, *p-xenyl*, *p-iodobiphenyl*, and *3,4-dimethoxyphenyl*. The commercially available isocyanates are: phenyl, *p*-bromophenyl, *p*-nitrophenyl,

α-naphthyl, and β-naphthyl. Phenyl isocyanate is a lachrymator and gives urethans that are somewhat soluble. Of the others, α-naphthyl is considered the most suitable. If it becomes necessary to use another urethan and the isocyanate is not commercially available, it is preferable to prepare the azide instead of the isocyanate; the preparation of aryl isocyanates involves treating an arylamine with phosgene, whereas the azide is prepared from the carboxylic ester. Thus, 3,5-dinitrobenzazide may be prepared by converting 3,5-dinitrobenzoyl chloride to the ethyl ester, treating the latter with hydrazine hydrate, and then reacting the resulting hydrazide with nitrous acid in the cold.

The degree of ease with which urethans are formed depends on the character of the radical attached to the hydroxyl group. Primary alcohols react with ease; secondary alcohols react slowly; and tertiary alcohols react with difficulty. As the rate of reaction with the isocyanate diminishes, the rates of the side reaction increase; thus, with the tertiary alcohols, olefin formation through dehydration may become the dominant reaction. The water produced by the dehydration of the alcohol reacts with the isocyanate in the manner indicated, and consequently the chief product may be a substituted urea instead of the desired urethan. The introduction of proton-repelling substituents in R-OH produce a retardation in the formation of urethans. Thus phenol, *m*-cresol, and thymol yield α-naphthylurethans readily, but *p*-nitrophenol with difficulty, even in presence of catalysts; picric acid does not react.

Equations (8) to (11) represent reactions used in the identification of phenols. In addition to the formation of urethans (shown in Equation (8)), the preparation of *benzoates*, *p-nitrobenzoates*, and *3,5-dinitrobenzoates* may be used. The formation of 3,5-dinitrobenzoates is usually accomplished by boiling the reaction mixture in pyridine. As previously mentioned, phenols react slowly with isocyanates. The reaction is catalyzed by small amounts of tertiary amines, such as trimethyl- or triethylamine. Phenols react rapidly with bromine to give bromo-substituted phenols, which in many cases form useful derivatives. Thus, phenol forms 2,4,6-tribromophenol, while *o*-cresol and *m*-cresol yield, respectively, dibromo and tribromo derivatives. Since bromination of phenols is relatively easy, the preparation of the bromo derivative should be considered. (For details on bromination, see pages 178–9). In the case of nitrophenols, the corresponding amino compounds obtained by reduction should be considered, because the formation of esters and urethans is slow and in some cases not feasible. For example, *p*-nitrophenol can be readily derivatized, even in 10 mg quantities, by catalytic reduction to *p*-aminophenol, as described on page 170.

Phenols react with chloroacetic acid in presence of sodium hydroxide to yield *aryloxyacetic acids*, as shown by Equation (9). The aryloxyacetic acids are crystalline solids having well-defined melting points; in addition, the determination of their neutralization equivalent may be used as a confirmatory test. For semimicro work it is necessary to have available at least 200 mg of the phenol; otherwise the yield is not sufficient for beginners to handle.

Equation (12) shows the formation of *2,4-dinitrophenyl ether* by the reaction of a phenol with 2,4-dinitrochlorobenzene. The phenol is dissolved in sodium hydroxide solution and is mixed with an alcoholic solution of 2,4-dinitrochlorobenzene. The mixture is refluxed for about one-half hour and diluted with water; the precipitated dinitrophenyl ether is filtered and crystallized from alcohol.

The following is a partial list of other derivatives that have been proposed for the identification hydroxy derivatives: (a) *xanthates* formed from aqueous solutions of the alcohol treated with potassium hydroxide and alcohol-free acetone and carbon disulfide at 40°; (b) *trityl ethers*, formed by treatment of the alcohol or glycol with triphenylmethyl chloride in presence of pyridine; (c) *p-toluenesulfonates* formed by reaction of the alcohol with *p*-toluenesulfonyl chloride; (d) *S-benzylthiouronium* derivatives formed by first converting the alcohol to the corresponding alkyl hydrogen sulfate with chlorosulfonic acid in presence of dioxane; the resulting alkyl hydrogen sulfates are then reacted with *S*-benzylthiouronium chloride; (e) *tetrachlorophthalates* by using tetrachlorophthalic anhydride in place of phthalic anhydride.

10.1 Ethyl-3,5-dinitrobenzoate. Place in an 8-inch tube 200 mg of pure 3,5-dinitrobenzoyl chloride and 0.3 ml of 95 per cent ethanol. Fit the tube with a microcondenser arranged for reflux and heat by means of a microburner so that the alcohol boils gently (avoid a hot flame) for 5 minutes. Cool for a minute and then add 3 ml of water. Cool and filter the crystals. Return the crystals to the test tube, add 5 ml of 5 per cent sodium carbonate solution, heat to about 60°, and then stopper the tube with a solid stopper and shake it vigorously for about 1 minute. Cool and filter; wash the crystals twice with 4–5 ml of water. Return the crystals to the tube, add 15 ml of ethanol, and heat until the cloudiness disappears. If the cloudiness persists near the boiling point of the solution, add alcohol dropwise. Cool for 10–15 minutes and filter. Wash twice with water and repeat the crystallization. About 100 mg of pure ethyl, 3,5-dinitrobenzoate are obtained, melting at 93°.

Note: Good results are obtained with 70 mg of 3,5-dinitrobenzoyl chloride and 0.1 ml of the alcohol. For example, 40 mg of pure *n*-propyl 3,5-dinitro-

benzoate melting at 73.5–74° were obtained after 1 crystallization from 0.1 ml of 1-propanol. In the case of alcohols having 6 or more carbon atoms, the heating of the reaction mixture should be prolonged to 10 minutes and, if the results are poor, the procedure described for the preparation of α-naphthyl 3,5-dinitrobenzoate should be used. When the quantity of alcohol available is but 1–2 drops, the procedure described for isobutyl 3,5-dinitrobenzoate is used. If the melting point of the dinitrobenzoate, after crystallization, is more than 2–4° below that recorded in the literature, proceed as described here. Dissolve the dinitrobenzoate (it need not be dry) in 5 ml of ethyl or isopropyl ether and wash the ethereal solution successively with 3 ml of 2 per cent sodium hydroxide solution and then with water. Evaporate the ether and crystallize the residue once from an alcohol-water mixture. If this method is applied to a crude sample of ethyl 3,5-dinitrobenzoate melting at 84–86°, a product is obtained melting at 92–93° without further crystallization. The 3,5-dinitrobenzoyl chloride should be pure if it is to be used in semimicro work. The method of preparation and purification is given on page 178. Commercially available chloride should be recrystallized from carbon tetrachloride unless the purity is specified. The stopper of the bottle in which the chloride is kept should be sealed with paraffin wax and exposure to air should be kept at a minimum.

10.2 Isobutyl 3,5-dinitrobenzoate. Place in a 6-inch tube 1–2 drops of isobutyl alcohol, 30 mg of 3,5-dinitrobenzoyl chloride, 5 ml of isopropyl ether (free from alcohol), and 1 drop of pyridine. Place a microcondenser within the tube so as to permit refluxing and heat in a beaker containing water for 1 hour; adjust the flame of the microburner so that the isopropyl ether boils gently (56°). Remove the tube from the water bath and cool in running water. Add 0.5–1 ml of dilute sulfuric acid and 4 ml of water. Stopper the tube with a solid rubber stopper and shake to remove the pyridine. Separate the ether layer either by transferring the liquid into a small separatory funnel or by inserting into the tube an appropriate separatory stopper (page 81). Wash the ether layer once with 1 ml of 10 per cent sodium hydroxide solution and twice with 4 ml of water to remove the dinitrobenzoic acid. Transfer the ether layer into a small casserole or evaporating dish; wash the vessel from which the ether solution was transferred with 1 ml of fresh isopropyl ether; and add the washings to the dish. Evaporate the ether carefully over a water bath; add to the residue 0.5 ml of alcohol and then 2 ml of water; and transfer the liquid into a small test tube. Cool for about 5 minutes and then scrape the sides of the tube with a glass rod. Filter the crystals and then wash them with 0.5 ml of water. The yield is 5–10 mg of crystals, melting at 85–86°.

Note: This procedure may be used whenever the quantity of hydroxy com-

pound is small or the hydroxy compound is not very reactive. For example, tertiary alcohols and phenols give good yields of dinitrobenzoates from 50–100 mg of the hydroxy compound. An alternative method for phenols is to use pyridine as a solvent, as described in the following procedure.

10.3 β-Naphthyl 3,5-dinitrobenzoate. Place in a 6-inch tube 150 mg of β-naphthol, 200 mg of 3,5-dinitrobenzoyl chloride, 2 ml of pyridine, and 2 boiling stones. Arrange for reflux and boil gently for 1 hour. Cool, add 1 ml of 5 per cent sulfuric acid and 5 ml of water; shake well and filter. Replace the crystals, together with filter paper, into the test tube, add 5 ml of two per cent sodium hydroxide, shake well to remove the 3,5-dinitrobenzoic acid, and filter; then wash twice with 2 ml of water. Suspend the crystals in 5 ml of methanol, heat almost to boiling, and filter. The crystals *remaining on the filter* are used for the melting-point determination. The yield is 130–150 mg, melting at 209–210°. A small crop of crystals may also be obtained from the filtered alcoholic solution.

Note: The solubility of the 3,5-dinitrobenzoates of naphthols in alcohol is small as compared with the like derivatives of phenols and cresols. For this reason the derivative is purified by removing soluble impurities, which in this case are mainly traces of dinitrobenzoic acid and unreacted naphthol. When the derivative separates out as an oil after washing with acid, the aqueous layer is poured out and 5–8 ml of ethyl ether or isopropyl ether are added, after which the ether solution is washed successively with water, 2 per cent sodium hydroxide solution, and finally with water. The ether is then evaporated and the residue is crystallized from methanol or ethanol.

10.4 Methyl p-nitrobenzoate. Place 0.2 ml of methanol and 100 mg of pure *p*-nitrobenzoyl chloride in a 6-inch tube and proceed as described under ethyl 3,5-dinitrobenzoate. Recrystallize the crude product by dissolving in 4–5 ml of hot methanol and adding 3 ml of water to the hot filtered solution. The yield is 90 mg melting at 95–96°.

10.5 n-Butyl 3-nitrophthalate. Place 200 mg of 3-nitrophthalic anhydride and 0.2 ml of *n*-butyl alcohol into an 8-inch test tube. Add 2 boiling stones and boil gently under reflux for 10–15 minutes. Pour 5 ml of water into the test tube and heat nearly to boiling, stirring the oil with a glass rod. Cool and pour off the aqueous layer from the oil adhering to the tube. Pour 10 ml of ethanol and 30 ml of water into the tube and heat to boiling. Decant the hot solution from any undissolved oil. Allow to cool overnight. Filter and wash with 20 per cent ethanol. The yield is 60–90 mg, melting at 145–146°.

Note: The nitrophthalates of methanol, ethanol, and the propanols form with greater ease and crystallize more readily. The melting points of the

nitrophthalates, after 1 crystallization, are sometimes 5–10° below the melting points given in the literature. This fact is due to incomplete reaction and to the presence of the isomeric ester. As many as 4 crystallizations are sometimes necessary.

10.6 n-Propyl α-naphthylurethan. Heat a 6-inch test tube over a flame until all moisture has been driven off; then cork and allow to cool. Put rapidly into the tube, by means of a pipette dropper, 0.2 ml of 1-propanol and 0.25 ml of α-naphthyl isocyanate; cork the tube immediately. Place the tube in a water bath at 60–70° for 5 minutes. Remove the tube and add 8 ml of petroleum ether (b.p. 90–110°) or 8 ml of commercial heptane. Heat to boiling and filter through a funnel prepared as follows: Insert the perforated disc inside of the funnel and place upon it a disc of filter paper; add 2 drops of water and apply light suction; then adjust filter paper. Add 3 drops of methanol and apply light suction again. Finally, add 4 drops of petroleum ether and repeat the application of suction. Fit the filter into the mouth of a clean and dry 8-inch test tube with a side-arm, apply suction, and add the hot solution containing the urethan. Cool the filtrate in cold water and scratch the sides of the tube by means of a glass rod. After 10 minutes, filter the crystals and crystallize from 5–6 ml of hydrocarbon. The yield is 80–90 mg of crystals, melting at 79–80°.

Note: It is necessary that the alcohol be free from water; otherwise a considerable amount of dinaphthylurea forms, with a corresponding decrease in the yield of the desired urethan. It is clear, therefore, that the preparation of the urethan should not be attempted unless it is known that the hydroxy compound is anhydrous. For secondary alcohols the duration of heating should be increased to 10 minutes. For example, from 0.2 ml of 2-butanol or 2-pentanol, 80–90 mg of the pure urethan are obtained. For smaller quantities of the hydroxy compound and for higher alcohols, the procedure described below is recommended.

10.7 Cyclohexyl α-naphthylurethan. Put 100 mg of cyclohexanol and 125 mg of α-naphthyl isocyanate into an 8-inch test tube dried as described in the preparation of *n*-propylurethan. Fit a two-hole stopper into the test tube holding a microcondenser and a calcium chloride tube. Add 6 ml of petroleum ether and heat in a water bath at about 90° for 30 minutes. Prepare a funnel as described in Section 10.6 above and filter the hot solution from the dinaphthylurea. Cool the solution for 10–15 minutes and then filter the crystals. Dissolve these in the minimum amount of hot petroleum ether and crystallize. The yield is 40–50 mg, melting at 128–129°.

Note: Tertiary alcohols react very slowly and yield but small amounts of urethans; dehydration of the alcohol occurs and results in increased formation of the dinaphthylurea. For example, 200 mg of *tert*-amyl alcohol with 0.25 ml of the isocyanate, treated as described in Section 10.6, gave 1.5 mg of a gummy substance that could not be purified for melting-point determination.

10.8 Thymyl α-naphthylurethan. Dry a test tube as directed in Section 10.6 above. While the tube is cooling, fit a cork (of a size equal to that with which the tube is stoppered) with a calcium chloride tube. Place rapidly in the dry test tube 200 mg of thymol and 0.25 ml of α-naphthyl isocyanate and stopper it with the cork holding the calcium chloride tube. Clamp the tube on a stand and heat it by means of a small direct flame so that the mixture boils gently for 2 minutes. Allow to cool for 3 minutes and then rub the mixture with a glass rod until it sets into a crystalline mass. Add 10 ml of petroleum ether, cool, and filter as described under the preparation of *n*-propylurethan in Section 10.6. Extract the residue with another portion of 8–10 ml of boiling petroleum ether. Filter the crystals and wash them with 1 ml petroleum ether. The yield is 120–140 mg of crystals, melting at 159°. On crystallizing from 7 ml of petroleum ether, 75–90 mg of pure urethan are obtained, melting at 160°.

Note: Nitrophenols do not yield urethans with ease. *p*-Nitrophenol, heated for 1 hour with the isocyanate, gives a product melting 30° below the temperature recorded in the literature as the melting point of the derivative. Naphthols react slowly, and therefore it is advisable to heat, under reflux, the naphthol and isocyanate dissolved in 5–10 ml of petroleum ether for 0.5–1 hour. Tertiary amines catalyze the reaction; a drop of 10 per cent solution of trimethyl, triethyl, or tributylamine in petroleum ether accelerates formation of urethans. The tertiary amine may be also used to induce crystallization in case the reaction mixture of phenol and isocyanate forms a viscous oil after heating.

10.9 Glyceryl tribenzoate. Place in an 8-inch test tube 100 mg (3 drops) of glycerol and add 0.5 ml of benzoyl chloride. Select a solid rubber stopper that fits securely in the mouth of the tube. Add 5 ml of 10 per cent sodium hydroxide solution and shake vigorously for 1 minute and then intermittently for 5 minutes or until the solid derivative separates out. Allow to stand in a cold bath for 30 minutes, shaking the tube at intervals so that the lumps forming at the beginning break up into small granules; use a rod for this purpose if necessary. Add 5 ml of water, shake vigorously for a minute, and then filter. Wash twice with 5 ml of water and place on a drying disc.

The recrystallization of the tribenzoate of glycerol and of the di-

benzoate of the glycols entails considerable difficulty, owing to the tendency of these esters (glycerides and glycol esters) to separate as oils. The following procedure gives fairly good results. Retain about 5 mg of the crystals and dissolve the rest in 10 ml of hot ethanol; then filter. Add 5 ml of water and reheat until the cloudiness disappears. Cool and add a few crystals from the lot set aside for seeding. Allow the tube to stand in the cold bath for 1–2 hours and then filter; wash twice with 2–3 ml of water and set aside to dry. The yield is 200–225 mg of crystals, melting at 75–76°. This derivative has also been reported to melt at 71–72°.

10.10 m-Toloxyacetic acid. Place in an 8-inch test tube 200 mg of *m*-cresol, 1 ml of 6 *N* sodium hydroxide solution, and 0.5 ml of a 50 per cent solution of chloroacetic acid. Provide the tube with a microcondenser arranged for reflux and heat in a water bath at 90–100° for about 1 hour. Cool and add 3 ml of water and 1 ml of 6 *N* hydrochloric acid. Extract with two 4-ml portions of ether; wash the combined ethereal solutions first with 2 ml of water and then with 5 ml of 10 per cent sodium carbonate solution, which removes the aryloxyacetic acid. Transfer the sodium carbonate solution into a beaker and add slowly dilute hydrochloric acid until the solution is distinctly acid. Cool and filter the crystals. The yield is 45–55 mg of crystals, melting at 101–2°.

10.11 Preparation of 3,5-dinitrobenzoates from aqueous solutions of alcohols. Take 5–10 ml of the solution that contains 250–500 mg of the alcohol. Dissolve separately 1 g of 3,5-dinitrobenzoyl chloride in 2 ml of specially purified ligroin (washed with H_2SO_4, then with H_2O, dried and distilled), and 8 ml of dry benzene. Place the alcoholic solution in an 8-inch tube, cool to 0°, and add 5 ml of the acid chloride solution and 500 mg of sodium acetate. Close tube with a No. 5 stopper, shake for 2 minutes with cooling (ice bath) so that the temperature remains below 5°. Place the tube in the ice bath for 30 minutes and shake it occasionally. Add 25 ml of ether, shake well, and separate the ether layer. Wash first with water, then with 5 ml of 5 per cent sodium hydroxide, followed by washing with 5 ml of 5 per cent hydrochloric acid solution and finally with water. Evaporate the ether solution and crystallize as in Section 10.1, page 221.

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Derivatives of Esters

In order to prepare derivatives for the final step of the identification of esters, it is necessary to *hydrolyze* them to their *acidic* and *hydroxy* components. The hydrolysis of semimicro quantities and isolation of 50–100 mg of an alcohol or an acid for derivatization require the utmost care. Even when the amount of ester used for hydrolysis is 2–3 g, the isolation of the hydrolytic products involves difficulties. The information obtained from the preliminary tests, boiling- or melting-point and refractive-index determinations, are of value in determining the probable nature of the ester; the type of hydroxy and acidic components present in the ester determines to a large extent the best method of procedure for the preparation of derivatives.

The most common esters are those of the lower alcohols having 1–4 carbon atoms. In the usual hydrolytic methods by aqueous alkali, the alcohol that is distilled after completion of hydrolysis contains a considerable amount of water and cannot be used for the preparation of nitrobenzoates or urethans. The preparation of benzoates through the Schotten-Baumann reaction is of little value for the lower alcohols, since these derivatives are chiefly liquids. On the other hand, the separation

of anhydrous, or nearly so, methanol or ethanol from 5–10 ml of aqueous distillate is an extremely difficult operation requiring apparatus not available to the beginner. The general procedure for the separation of an alcohol is to saturate the distillate with potassium carbonate and then extract with ether (free from alcohol). This procedure gives fair results when the amount of ester is 5–10 g but is not satisfactory for the esters of lower alcohols, when the amount of ester hydrolyzed is less than 2 g.

Difficulties are also encountered in the identification of the acidic group of the esters. The common procedure is to evaporate the alkaline residue after distillation or extraction of the hydroxy compound and to use the sodium salt for the preparation of the *p*-toluidide, anilide, or other suitable derivative of the acid derived from the ester. The presence of excess alkali, however, complicates the preparation of such derivatives; as a consequence, even when one starts with 1 g of ester, little or no derivative of the acid is obtained with the use of such methods. This is particularly true in the case of the esters of the lower aliphatic carboxylic acids.

Consideration must be given to the effect of the excess alkali used in the hydrolysis upon labile functional groups such as are encountered in the β-keto esters, and in the esters of halogen acids; for example, alkali hydrolysis of ethyl acetoacetate will produce cleavage on the acetoacetic acid with the formation of acetone; similarly, alkaline hydrolysis of either α-chloro or α-bromobutyrates will give rise to both crotonic and α-hydroxybutyric acids.

Finally, esters hydrolyze at vastly different rates. Most esters of alcohols with less than 4 carbon atoms hydrolyze when they are treated for 30 minutes or less with hot 6 N sodium or potassium hydroxide solution. Esters boiling above 200° require from 1–2 hours for complete hydrolysis. The disappearance of the ester layer cannot be used as a criterion for completion of hydrolysis of compounds that are slightly miscible with water; as the hydrolysis proceeds, the hydroxy compound formed rises to the top and therefore, even at the completion of hydrolysis, there remains an immiscible layer.

From this brief discussion it is evident that the exact procedure to be followed in the hydrolysis of esters and identification of the hydroxy and acyl radicals depends on the nature of the ester. The recommended procedures for semimicro quantities (using 200 mg of the ester) are briefly summarized.

1. If the ester boils below 150°, the hydroxy compound is identified by boiling 200 mg of the ester with 500 mg of 3,5-dinitrobenzoyl chloride dissolved in 2–3 ml of anhydrous pyridine. The 3,5-dinitrobenzoate

formed is separated from pyridine and the excess of dinitrobenzoyl chloride and dinitrobenzoic acid; the residue cannot be used for identification of the acyl radical because it contains a considerable amount of 3,5-dinitrobenzoic acid.

2. If the ester boils above 150°, it is saponified with a solution of potassium hydroxide dissolved in diethylene glycol. After hydrolysis (about 10 minutes), the alcohol is distilled and used for the preparation of a derivative. The residue is used for the identification of the acid. Another method is to use hydrolysis with aqueous alkali but the time required for the hydrolysis is 1–2 hours. The mixture is then extracted with isopropyl ether to remove the alcohol, while the residue is used for the identification of the acid.

3. For the identification of the carboxylic compound, the procedure depends on the nature of the acid.

(a) If the acid is a solid, the ester is hydrolyzed by boiling with 6 *N* potassium hydroxide; the salt is converted to the acid, which is identified by its melting point or, if necessary, by preparation of the anilide or toluidide.

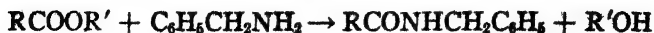
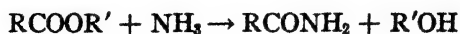
(b) If the acid is a liquid with less than 6 carbon atoms, the *p*-toluidide or the anilide may be prepared directly from the ester by means of the Grignard reaction. Ethyl magnesium bromide is prepared and then reacted with *p*-toluidine or aniline and then boiled with the ester; the reaction is discussed in the section on Grignard reagents (page 189) and illustrated by the preparation of aceto-*p*-toluidide (page 233).

(c) If the acid is a liquid and is insoluble in water (such as the higher fatty acids) and the preparation of the *p*-toluidide through the Grignard reagent does not yield satisfactory results, the best procedure is to hydrolyze the ester. If aqueous potassium hydroxide is used, the solution is acidified and the residue is extracted with benzene. A slight excess of thionyl chloride is added to convert the carboxylic compound to the acid chloride and the *p*-toluidide or anilide is prepared by methods that are described in Section 9.3, page 210. If potassium hydroxide dissolved in diethylene glycol is used to effect the hydrolysis of the ester, the residue is treated according to the procedure described in Section 10.13.

(d) The acidic component of the ester may be identified by reaction with aqueous ammonia, benzylamine, or hydrazine hydrate, as shown by the following equations:

$$RCOOR' + NH_3 \rightarrow RCONH_2 + R'OH$$

$$RCOOR' + C_6H_5CH_2NH_2 \rightarrow RCONHCH_2C_6H_5 + R'OH$$

$$RCOOR' + HNHNH_2 \rightarrow RCONHNH_2 + R'OH$$

The products are: amides, benzamides, and hydrazides; the solubility of the amides renders the reaction with ammonia unsuitable in most cases. The preparation of benzamides is effected by boiling benzylamine with the ester. Halogenated esters yield benzylamine hydrohalides by this treatment:

$$XCH_2COOR + 2C_6H_5CH_2NH_2 \rightarrow C_6H_5CH_2NHCH_2COOR + C_6H_5CH_2NH_3^+X^-$$

A recent modification[1] of the reaction of esters with benzylamine avoids the use of water and employs ammonium chloride as a catalyst; this method has been applied successfully to the identification of about 65 acyl groups in esters, using about 1 ml of the liquid ester. For details of the method and melting points of the N-benzylamides, the reader is referred to the original article.

Alkyl nitrites, nitrates, and sulfates. A few of the esters of the lower alcohols and inorganic acids, which are used occasionally in the organic laboratory, are listed in the tables on esters. (**Caution:** *Exercise care in handling these compounds as most of them have toxic effects.*) The nitrites hydrolyze very readily and may be detected by the ease with which they diazotize aniline in presence of glacial acetic acid, or by the addition of 2-phenylindole, which forms a precipitate of *3-isonitroso-2-phenylindole.* The three common nitrites are ethyl, *n*-butyl, and isoamyl; the alcohol is readily identified after hydrolysis by the usual methods. The sulfates are characterized either by the preparation of *phenyl ethers* or by conversion to the *thiouronium derivatives*, as outlined in Section 13.17, page 324.

Lactones. These compounds are listed under esters because they are formed by the reaction of the carboxyl and hydroxyl groups of the same molecule; it is quite probable, however, that the lactones will be detected as acidic compounds by the functional group tests, since they undergo hydrolysis to yield hydroxycarboxylic acids. The most common compounds of this group are: (a) ascorbic acid, a lactone of a sugar unsaturated acid (see page 453); (b) γ-butyrolactone, which is easily derivatized by ammonolysis forming γ-hydroxybutyramide.

The examples described in the following section illustrate some of the methods that have been proposed. It should be again emphasized, however, that the particular procedure to be followed depends on the nature of the hydroxy and acid components of the ester. The reader is also referred to the section on hydrolysis in Chapter 8.

[1] Dermer and King, see Bibliography, page 234.

The procedure for determining the saponification equivalent of an ester is given in the Appendix (page 469). Since the iodine number is often determined for oils and fats, a method for the determination of the iodine number is also given in the Appendix (page 470).

10.12 Identification of isopropyl acetate. Place 300 mg of isopropyl acetate, 500 mg of 3,5-dinitrobenzoyl chloride, and 3 ml of pyridine in an 8-inch tube, provided with a condenser arranged for reflux. Add 2 small boiling stones and heat for 1.5–2 hours over a small flame so that the mixture boils gently. Cool and add a mixture of 1 ml 6 *N* sulfuric acid and 9 ml of water (10 ml of 3 per cent acid). Cool and shake the mixture vigorously; extract the mixture with 5 ml of isopropyl ether or 5 ml of ethyl ether, which has been washed with water, placed over calcium chloride and sodium, and then filtered (to remove all traces of ethanol). Separate the ether layer and wash it first with 5 ml of 2–3 per cent sulfuric acid, then with 4 ml of 2 per cent sodium hydroxide solution, and finally with 3 ml of water. Evaporate the ether layer from a small dish. Dissolve the residue in 5 ml of methanol, add a minute amount of charcoal, filter, and add to the filtrate 2 ml of water. About 60–70 mg of crystals separate out, melting at 116–118°. Dissolve the solid in 4 ml of methanol and precipitate with 1.5 ml of water. Filter and dry the 3,5-dinitrobenzoyl ester of isopropyl alcohol. The yield is 30–45 mg of crystals, melting at 121–122°.

For the identification of the acidic part of the ester, a new portion of the ester is hydrolyzed. Place 300 mg of the ester, 0.3 g (1 pellet) of potassium hydroxide, 1 ml of water, and 1 boiling stone. Boil for 15 minutes and then dilute to 2 ml with water; add 1 ml of 6 *N* hydrochloric acid and 1 drop of phenolphthalein; if the solution is acid, add sodium hydroxide solution (5–10 per cent, until the color of the solution is just pink). Add 2 drops of 5 per cent hydrochloric acid so that the pink color is discharged. If the original solution is alkaline, add dilute hydrochloric acid (5–10 per cent) until the color of phenolphthalein just fades. Add 200 mg of *p*-nitrobenzyl bromide or chloride and 8 ml of methanol and a small boiling stone. (**Caution:** *Be careful in handling p-nitrobenzyl halides.*) Arrange a reflux condenser for the tube and boil gently for 1.5 hours. Cool and add 2–3 ml of water; by means of a glass rod scratch the inner sides of the tube. After 20 minutes filter the ester and wash first with 4 ml of 5 per cent sodium carbonate and then twice with 2 ml of water. Crystallize according to the method described in Procedure 9.7, page 212. The yield is 40 mg, melting at 77–78°.

10.13 Identification of butyl phthalate. Place in an 8-inch distilling

tube 1.5 ml of diethylene glycol, 0.3 g (1 pellet) of potassium hydroxide, and 5 drops of water. Heat by means of a small flame until the pellet dissolves. Cool by means of tap water to room temperature and add 0.5 ml of the ester. Arrange tube with a reflux condenser and connect the outlet with a condensing setup (Figure 20). Heat to gentle boiling, shaking the tube from time to time; when the ester layer disappears (3–5 minutes), the reflux condenser is removed and 2 ml of dry pyridine are added. The tube is carefully heated until 2.2 ml of distillate have been collected. The distillate is used to prepare the 3,5-dinitrobenzoate, as described in Section 10.3, page 223. The residue is diluted with 5 ml of water and then acidified with 6 *N* sulfuric acid. The crystals that separate out are filtered and the melting point determined.

If a derivative of the acid is desired, the residue left in the distilling flask is diluted with 5 ml of water and 5 ml of ethanol and then neutralized to phenolphthalein with 6 *N* sulfuric acid; it is then set aside to permit separation of potassium sulfate. The mixture is filtered and the clear filtrate is used for the preparation of *p*-nitrobenzyl ester (10.12).

10.14 Aceto-p-toluidide from ethyl acetate. Read the discussion of the preparation on page 189. Prepare the Grignard reagent according to the directions given in procedure 8.41, page 191, and observe all the precautions as to removal of moisture from the apparatus and reagents. Use 1 g of magnesium, 5 ml of absolute ether, and 500 mg of ethyl bromide. When practically all the magnesium has dissolved, cool and add slowly a solution of 500 mg of *p*-toluidine in 4 ml of ether; after a minute add 0.2 ml of ethyl acetate and reflux the mixture for 5–10 minutes. Cool and hydrolyze with 5 ml of dilute hydrochloric acid. Separate the ether layer and wash it first with dilute hydrochloric acid and then with water. Evaporate the ethereal solution and dissolve the residue in 2 ml of boiling ethanol. Filter and add 1 ml of water to precipitate the aceto-*p*-toluidide. The yield is 30–35 mg of crystals, melting at 146–7°.

10.15 Triphenyl phosphate. Place in an 8-inch tube 0.3 g (1 pellet) of potassium hydroxide, 1 ml of water, 200 mg of the solid ester, and 1 boiling stone. Boil gently for 15 minutes; dilute to 4 ml with water and cool. Remove 1 ml into an 8-inch tube and add 2 ml of water, 1 ml of 6 *N* nitric acid, and 1 ml of ammonium molybdate solution, in the order given. Allow to stand for 5 minutes; a yellow precipitate indicates the presence of phosphate.

Acidify the remaining 3 ml of the hydrolyzed solution by means of dilute hydrochloric acid. Brominate according to Section 8.26, page 179, to identify phenol.

Selected References on Esters

Preparation of p-toluidides from esters. Koelsch and Tanenbaum, *J. Am. Chem. Soc.*, **55**, 3049 (1933).

Preparation of anilides from esters. Hardy, *J. Chem. Soc.*, **1936**, 398.

Hydrazides as characteristic derivatives for the identification of esters. Sah, *Rec. trav. chim.*, **59**, 1036 (1940).

Removal of acyl groups. Baltzly and Buck, *J. Am. Chem. Soc.*, **63**, 2022 (1941).

N-Benzylamides as derivatives for identifying the acyl group in esters. Dermer and King, *J. Org. Chem.*, **8**, 168 (1943).

Rapid saponification of esters by potassium hydroxide in diethylene glycol. Redemann and Lucas, *Ind. Eng. Chem., Anal. Ed.*, **9**, 521 (1937).

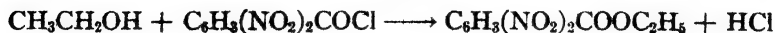
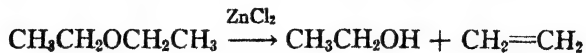
Derivatives of Ethers

The ethers are relatively inert compounds; the carbon-oxygen bond in ethers cannot be easily split and hence the preparation of derivatives from semimicro quantities involves some difficulties. In the case of aromatic ethers, it is possible by bromination or through other substitution reactions to prepare suitable solid derivatives that may be used for characterization. For the derivatization of aliphatic ethers, however, it is necessary to cleave the ether linkage in order to prepare a derivative of the resulting hydroxy compound.

Two general methods have been proposed for the splitting of ethers. The first method employs heating in the presence of anhydrous zinc chloride and 3,5-dinitrobenzoyl chloride. The ether becomes cleaved to the hydroxy compound, which reacts with the acid chloride to give the 3,5-dinitrobenzoate. The first step in the cleavage is assumed to be the formation of an alcohol and an olefin; the alcohol thus formed reacts with 3,5-dinitrobenzoyl chloride to give the ester and hydrogen chloride; the latter converts some of the alcohol into an alkyl chloride.

$$CH_3CH_2OCH_2CH_3 \xrightarrow{ZnCl_2} CH_3CH_2OH + CH_2{=}CH_2$$

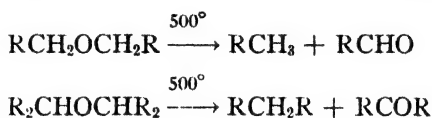
$$CH_3CH_2OH + C_6H_3(NO_2)_2COCl \longrightarrow C_6H_3(NO_2)_2COOC_2H_5 + HCl$$

$$CH_3CH_2OH + HCl \longrightarrow CH_3CH_2Cl + H_2O$$

Aside from the reactions that diminish the amount of 3,5-dinitrobenzoate, the chief difficulty of the method as applied to micro and semimicro quantities is that a number of aliphatic ethers boil at low temperatures and prolonged heating results in considerable losses of the com-

pounds before cleavage is effected. The amount of 3,5-dinitrobenzoate obtained from a series of experiments with 0.5 ml of ethyl ether and isopropyl ether was often less than 10 mg, while in many runs no derivative at all was obtained. It has been observed that, if the zinc chloride is freshly fused and precautions are taken to dry thoroughly the tube and microcondenser, better yields are obtained. By the use of a sealed tube and heating under pressure, it is possible to prevent the loss of the ether and obtain a sufficient amount of the derivative.

The second method of cleavage utilizes vapor phase pyrolysis; when an ether is pyrolyzed in the vapor phase, the chief products are a hydrocarbon and an aldehyde or ketone, as shown by the following equations:

$$RCH_2OCH_2R \xrightarrow{500^\circ} RCH_3 + RCHO$$

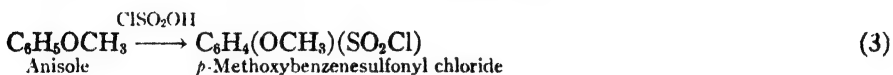
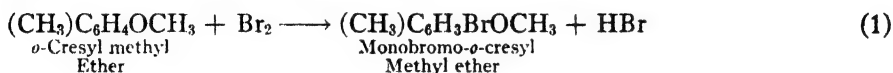
$$R_2CHOCHR_2 \xrightarrow{500^\circ} RCH_2R + RCOR$$

The aldehydes or ketones produced by the pyrolysis are identified by preparation of the semicarbazone, or substituted phenylhydrazones. Since this method involves special equipment and techniques, it is not recommended as the first procedure to be used by the beginner.

The chief reactions to be used for the preparation of derivatives from aromatic ethers are illustrated by the following equations:

$$\underset{\text{o-Cresyl methyl Ether}}{(CH_3)C_6H_4OCH_3} + Br_2 \longrightarrow \underset{\text{Monobromo-o-cresyl Methyl ether}}{(CH_3)C_6H_3BrOCH_3} + HBr \quad (1)$$

$$\underset{\text{Anisole}}{C_6H_5OCH_3} + \underset{\text{Picric acid}}{C_6H_2(NO_2)_3OH} \longrightarrow \underset{\text{Anisole picrate}}{C_6H_5OCH_3 \cdot C_6H_2(NO_2)_3OH} \quad (2)$$

$$\underset{\text{Anisole}}{C_6H_5OCH_3} \xrightarrow{ClSO_2OH} \underset{\text{p-Methoxybenzenesulfonyl chloride}}{C_6H_4(OCH_3)(SO_2Cl)} \quad (3)$$

$$C_6H_4(OCH_3)SO_2Cl \xrightarrow{NH_3} \underset{\text{p-Methoxybenzenesulfonamide}}{C_6H_4(OCH_3)SO_2NH_2} + NH_4Cl \quad (4)$$

Equation (1) represents the bromination of the aromatic ether; the compound is dissolved in glacial acetic acid, alcohol, or chloroform and the required amount of bromine is added dropwise. The *bromosubstituted* ether is obtained either by addition of water or evaporation of the solvent. The extent of bromination depends on the groups already present: *o*-cresyl methyl ether forms a monobromo, whereas guiacol (1-methoxy-2-hydroxybenzene) forms a tribromo-derivative. Ethers that have an unsaturated linkage undergo addition and substitution; thus anethole (*p*-propenylphenyl methyl ether) forms a monobromo dibromide.

Equation (2) represents the formation of a *molecular compound* with picric acid. The picrates form readily by mixing equimolecular amounts of the ether and picric acid dissolved in the minimum amount of warm chloroform, and then allowing the mixture to stand for a short time. Although a number of the picrates are unstable on exposure to air, their preparation offers a relatively convenient method for identification of a number of aromatic ethers. Since halides, when treated with β-naphthol, form *naphthyl ethers* readily, which may be identified by the picrates, the method may be employed for the derivatization of a number of alkyl halides.

Equation (3) represents the conversion of an aromatic ether to a *substituted benzenesulfonyl chloride* through reaction with chlorosulfonic acid; the sulfonyl chloride is converted by ammonolysis to the substituted *benzenesulfonamide* (as shown in Equation (4)), which may be identified through its melting point. The method is feasible when the preparation of a bromo derivative or a picrate does not afford satisfactory results. The original papers (listed in the Bibliography) should be consulted.

Other reactions of aromatic ethers that may be used for the preparation of derivatives are nitration and oxidation. Oxidation is used in the case of ethers having side-chains—as, for example, the cresyl ethers; these, by oxidation, yield alkoxybenzoic acids. With few exceptions both nitration and oxidation give poor yields of derivatives.

Caution: When ethers are used, it is well to bear in mind that they form *peroxides* easily, particularly, when exposed to light and air. The peroxides detonate when heated, and hence the distillation of an appreciable amount of ether, which contains peroxide, involves the danger of an explosion if the distillation is allowed to proceed to dryness. The presence of peroxides in ethers is detected by means of starch iodide paper that has been moistened with dilute hydrochloric acid. The peroxides are removed by washing the ether with water containing a small amount of ferrous sulfate and dilute sulfuric acid. For small quantities of ethers, as, for example, 10 ml, washing with 2-3 ml of water containing 5 drops of 10 per cent solution of ferrous sulfate and 1 drop of sulfuric acid is sufficient.

10.16 Identification of isopropyl ether. Heat a 6-inch tube in a strong flame until all the moisture has been removed; cork while hot and allow to cool. Prepare fused zinc chloride as directed in Procedure 10.18. Place a piece of paper on the balance and determine the weight of zinc chloride transferred by a semimicro spatula filled to the top. The bottle is opened and closed rapidly so as not to expose the fused powdered material to moisture. After the weight has been determined, the zinc

chloride is washed into the sink, the paper placed in the waste jar, and the spatula is cleaned and dried.

By means of the spatula, transfer rapidly 500–700 mg of zinc chloride into the dry tube by raising the cork momentarily; add 0.5 ml of isopropyl ether and 250 mg of 3,5-dinitrobenzoyl chloride. The cork holding the microcondenser is rapidly inserted into the mouth of the tube after the condenser has been thoroughly wiped off to remove the film of moisture. The cork holding the condenser should be provided with an opening holding a calcium chloride tube. The reaction tube is immersed in a water bath kept at 60–65° and heated at such rate that the vapors of the ether do not condense much above the end of the microcondenser. Heat for 2 hours or until very little liquid condenses at the sides of the tube.

Remove the tube from the water bath and add 5 ml of 10 per cent sodium carbonate solution heated previously to 60–70°. By means of a glass rod stir the solid on the bottom of the tube. Shake the mixture at intervals for about 2–3 minutes; then filter by suction. Wash the solid once with 5 ml of sodium carbonate solution and twice with 5-ml portions of water. Dry the solid by suction as far as possible and transfer it by means of the spatula into a dry test tube. Add 5 ml of carbon tetrachloride and boil gently over a small flame of the microburner. Continue the boiling for about 2 minutes; then filter rapidly by suction. Pour the filtrate into a small evaporating dish and remove the solvent on the water bath. Wash the tube in which the filtrate was received with 1 ml of solvent and add washings to the dish. When all the solvent has been evaporated, remove the dish from the water bath and add 1.5 to 2.0 ml of methanol; rotate the dish so that the solvent comes in contact with any solid or oil on the sides. Pour the methanol solution into a tube and wash the dish with an additional 0.5–1.0 ml of solvent and unite washings with the main portion of the solution. Add water dropwise until a permanent cloudiness results; then cool and rub the inner sides of the tube by means of a glass rod. After 10 minutes filter the solid and crystallize from the minimum amount of methanol, using the same procedure for precipitation. The yield varies from 10–30 mg. The melting point, after the first crystallization, is usually 120–1°. When the extraction is faulty, the melting point of the crystals may be as low as 110–115°.

Note: It is not unusual for the yield to be less than one milligram. If the heating of the mixture is not controlled, the ether will escape before it is cleaved by the zinc chloride. This is particularly true of ethyl ether; the mixture in this case must be kept at 35–36° and, since this is difficult to achieve, volatili-

zation occurs. Heating in a closed tube, as outlined in the next experiment, requires care and time but gives better results.

10.17 Identification of an ether by heating under pressure. Prepare a tube of Pyrex glass 8 mm in diameter and 120–130 mm in length, closed at one end. Dry the tube by rotating it in a semiluminous flame; then cork and allow to cool. After 15 minutes, cool the lower end of the tube and introduce the ether, zinc chloride, and 3,5-dinitrobenzoyl chloride, as directed in the preceding experiment. Hold the closed end of the tube (by means of a small piece of asbestos paper) with the left hand and heat the open end over a small smoky flame of the blast lamp. Rotate the tube and, after it has been heated for 1–2 minutes, increase the size of the flame and turn on the air or oxygen until a good blue flame has been obtained. Grasp with the right hand a glass rod or Pyrex tubing 6–8 mm in diameter and about 150 mm long and heat it in the zone of the flame opposite the region in which the tube is heated. When the glass in both tube and rod is near the fusion point, press the rod lightly against the inside wall of the tube. Adjust the flame quickly to a narrow point and heat the junction until the glass is fused and a good seal is obtained. Shut off the air and heat the tube over the smoky flame for a few minutes; then align the tube and rod. Wet the asbestos paper by which the closed end of the tube is held in ice-cold water. Increase the flame and heat the tube about 30 mm below the seal. As the glass softens, the wall of the tube grows thicker in the region heated by the intense flame. While holding the tube in the left hand at an angle of 45°, rotate it continuously with the right hand. When the inside diameter of the tube has been reduced to about half, withdraw the tube to a short distance above the flame and draw the end out cautiously until the constricted part has attained a length of about 15–20 mm and a diameter of about 2–3 mm. Then remove the tube from the flame and, holding it vertically, slowly draw out the thickened part to form a capillary. Adjust the flame quickly to a narrow point and direct it against the capillary, holding the tube slightly inclined. While the flame is being adjusted, the lower end of the tube is cooled. Seal off the tube by cautiously pulling apart the upper portion of the tube. Shut off the air at once and direct the smoky flame against the capillary. It is best to clamp the tube and allow a small smoky flame to play upon the capillary for 5–10 minutes; the tube is allowed to cool.

Wrap the tube tightly in a small piece of paper and twist the ends. If a bomb furnace is available, place the tube in the iron jacket with the capillary at the open end. Place the tube in the bomb furnace in accordance with instructions posted in the bomb furnace room. Place the

thermometer in the top of the furnace. Raise the temperature gradually in about 20 minutes to 100–110° and adjust the heating so that the temperature does not rise higher. Note the temperature every 10 minutes and heat for 1 hour. When cold, remove tube and open according to directions posted in the bomb room or as directed below.

If a bomb furnace is not available, place the wrapped tube in a piece of iron pipe 0.5 inches in diameter and 6–8 inches in length such as may be obtained from any hardware store. Stopper each end of the pipe with an old two-hole rubber stopper. Prepare a water bath from an empty one-gallon tin can. Remove the top with a can opener and hammer the edges inward. (**Caution:** *Wear canvas gloves while opening the can to guard against cuts.*) Place the can in the hood on 4 bricks so arranged that a flat burner will fit underneath; or place the can on a solid tripod. Put the pipe with the tube upright in the can and add water until the level is above the three-quarter mark. When more than one tube is to be heated, the short pieces of pipes are provided with metal tags that have numbers stamped on them. Place a cover (wood or Transite) on top of the can and heat the water to boiling. Adjust the flame so that the boiling is gentle and little steam escapes. No further attention need be paid unless the tube explodes. This usually happens if the seal was not properly made or if a strain was placed on the glass in making the seal. If more than one tube explodes at the same time, the force of the explosion may be sufficient to displace and tilt the can slightly, if a tripod is used, so that the water may put the burner out. Should an explosion occur, the gas should be turned off and the bath inspected. The tube is heated in the boiling bath for 2 hours.

Remove the pipe after the bath has cooled and drain the water. Holding it in a horizontal position, place it flat on the floor of the hood. (**Caution:** *Wear goggles.*) Remove the rubber stoppers and with a rod gently push the tube so that the capillary just projects out of the pipe. Insert some crumpled paper at the other end and insert the stopper so that, when the pipe is placed upright, the end of the capillary protrudes about 10 mm above the mouth of the pipe. Clamp the pipe securely on an iron stand so that the lower end of the pipe dips into a liter beaker containing an ice-salt mixture. Heat the extreme end of the capillary by means of a strong, pointed flame. If, on softening, the glass it not blown out, allow to cool for a minute or so and then touch the heated part by means of a wet piece of cotton wrapped at the end of a rod. If the upper end of the capillary does not crack, reheat and repeat the application of water. Knock off the cracked end of the capillary with a file. Allow the glass to cool and remove the tube from the pipe.

Wash the inner sides of the tube with 2 ml of water; then cut the lower end of the tube containing the reaction mixture and place it in an 8-inch tube. If some of the reaction mixture adheres to the sides of the upper portion of the tube, it is cut and extracted. Add 5 ml of hot sodium carbonate solution so that the small reaction tube resting at the bottom of the 8-inch tube is filled; then proceed to isolate and purify the 3,5-dinitrobenzoate, as directed in the preceding Section 10.16, page 236.

10.18 Preparation of fused zinc chloride. Use an iron crucible or dish 20–40 mm in diameter. Place in the dish about 10 g of technical powdered zinc chloride. Put the crucible or dish on a tripod and heat with a strong flame. Stir the fused mass with a long screw driver or an appropriate iron rod, while holding the crucible by means of tongs. Scrape the material that solidifies on the sides and push it toward the center. When the whole has melted and no bubbles arise from the melt, discontinue heating. Hold the crucible firmly by the lip with the tongs and remove it from the tripod on to an asbestos mat. Stir the melt with the screw driver as it cools. When the melt begins to solidify, scrape it away from the sides of the dish. In this manner the zinc chloride solidifies in a dough-like consistency that does not adhere to the sides. Keep stirring the dough-like solid until it begins to crumble. At this point use a pestle and, holding the dish down firmly with the tongs, pulverize the lumps to a fine powder. If the solid is still dough-like, use the screw driver again to stir for a minute or so; then use the pestle. The zinc chloride pulverizes into a freely running fine powder that is still hot. Empty the dish on a large piece of paper and transfer the powder rapidly into a dry bottle that has been previously warmed. Close the bottle, using a tightly fitting bakelite screw cap. When needed, the chloride is weighed rapidly and added to the reaction mixture at any time. The dish is cleaned by soaking with water and then dried. Rust does not interfere with the activity of zinc chloride.

10.19 Bromination of 2-naphthyl methyl ether. Place in an 8-inch tube 200 mg of 2-naphthyl methyl ether (β-naphthyl methyl ether) and 3 ml of glacial acetic acid. Place the tube in cold water and add with *caution* 3 drops (240 mg) of bromine at the rate of 1 drop per minute. Remove the tube from cold water, cork, and allow to stand for 10 minutes. Add 20 ml of water and filter the crystals of the dibromo compound. Wash with water and transfer the solid into a test tube. Add 5 ml of alcohol and heat until most of the solid dissolves, adding dropwise more alcohol until complete solution is effected. Filter and add water to the filtrate until a permanent cloudiness results. Cool and

filter the solid. About 250–300 mg of crystals, melting at 62°, are obtained.

Note: The same conditions of bromination may be employed for certain aromatic ethers but not for all; for example, the bromination of anethole described in 10.20 is best carried out in the presence of an anhydrous aliphatic ether. In general, the aromatic ether is dissolved in glacial acetic acid, alcohol, or chloroform and a slight excess of bromine is added slowly while the reaction mixture is cooled.

If alcohol or glacial acetic acid is used as a solvent, the bromo compound is separated by addition of water; if the bromo compound tends to separate as an oil on addition of water, the procedure of separation is altered. The solvent is evaporated and the crude solid is crystallized from alcohol, petroleum ether, or isopropyl ether.

10.20 Bromination of anethole. Place in an 8-inch test tube 100 mg of anethole and 2 ml of isopropyl ether (or absolute ethyl ether). Cool in an ice bath or tap water and add dropwise, over a period of 5 minutes, a solution of 240 mg of bromine (3 drops) in 2 ml of ether. Allow to stand 5 minutes; then filter the crystals. Dissolve the solid in 8–10 ml of boiling petroleum ether, filter, and cool the filtrate. Filter and dry the solid; the yield is 150–180 mg of crystals, melting at 107°.

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Preparation of Derivatives—Continued

Derivatives of Carbonyl Compounds

ALDEHYDES and ketones react readily with such reagents as phenylhydrazine, semicarbazide, and hydroxylamine to form derivatives that are useful in characterization work. The more important types of derivatives are illustrated by the following equations:

$$\underset{}{\overset{H}{RC}}{=}O + \underset{\text{Phenylhydrazine}}{H_2NNHC_6H_5} \longrightarrow \underset{\text{Phenylhydrazone}}{\overset{H}{RC}{=}NNHC_6H_5} + H_2O \qquad (1)$$

$$\overset{H}{RC}{=}O + \underset{p\text{-Nitrophenylhydrazine}}{H_2NNHC_6H_4(NO_2)} \longrightarrow \underset{p\text{-Nitrophenylhydrazone}}{RCH{=}NNHC_6H_4(NO_2)} + H_2O \qquad (2)$$

$$(CH_3)_2C{=}O + \underset{2,4\text{-Dinitrophenylhydrazine}}{H_2NNHC_6H_3(NO_2)_2} \longrightarrow$$
$$\underset{\text{Acetone 2,4-dinitrophenylhydrazone}}{(CH_3)_2C{=}NNHC_6H_3(NO_2)_2} + H_2O \qquad (3)$$

$$\overset{H}{C_6H_5C}{=}O + \underset{\text{Semicarbazide}}{H_2NNHCONH_2} \longrightarrow \underset{\text{Benzaldehyde semicarbazone}}{\overset{H}{C_6H_5C}{=}NNHCONH_2} + H_2O \qquad (4)$$

$$(CH_3)_2C{=}O + \underset{\text{Hydroxylamine}}{H_2NOH} \longrightarrow \underset{\text{Acetoxime}}{(CH_3)_2C{=}NOH} + H_2O \qquad (5)$$

$$2(CH_3)_2C\left\langle\begin{matrix}CH_2{-}CO\\CH_2{-}CO\end{matrix}\right\rangle CH_2 + RCHO \longrightarrow$$
Methone
(Dimethylcyclohexanedione)

$$(CH_3)_2C\left\langle\begin{matrix}CH_2{-}CO\\CH_2{-}CO\end{matrix}\right\rangle CH{-}\overset{R}{\underset{H}{C}}{-}C\left\langle\!\!\begin{matrix}CO{-}CH_2\\ \| \\ \underset{OH}{C}{-}{-}CH_2\end{matrix}\right\rangle C(CH_3)_2 + H_2O \qquad (6)$$
Methone derivative[1]

$$\underset{m\text{-Nitrobenzaldehyde}}{C_6H_4(CHO)(NO_2)} \xrightarrow{[O]} \underset{m\text{-Nitrobenzoic acid}}{C_6H_4(COOH)(NO_2)} \qquad (7)$$

Equations (1), (2), and (3) represent the formation of *phenylhydrazones*

[1] The structure shown is for the normal derivatives; a variety of reagents produce cyclization to yield octahydroxanthenes.

and *substituted phenylhydrazones.* Of the many substituted hydrazones that have been proposed, the *2,4-dinitrophenylhydrazones* and *p-nitrophenylhydrazones* are recommended for semimicroquantities whenever the melting points of the derivatives are not much above 200°. Among the other substituted hydrazones that have been proposed in the literature as suitable derivatives of aldehydes and ketones are: *o, m,* and *p-chlorobenzohydrazones; p-nitrobenzohydrazones; diphenylhydrazones; β-naphthylhydrazones; o, m,* and *p-nitrobenzenesulfonhydrazones; p-carboxyphenylhydrazones; α-(2,4-dinitrophenyl)-α-methylhydrazones;* and *nitroguanylhydrazones.*

Since phenylhydrazine is easily available and the derivatives form readily, the use of phenylhydrazones, particularly for the aryl carbonyl compounds, is advisable. For the preparation of the derivatives, the carbonyl compound is dissolved in methanol or ethanol and heated with phenylhydrazine base and a small amount of acetic acid; the phenylhydrazone separates even while the solution is hot. After filtration the derivative should be dried rapidly and the melting point determined at once, since phenylhydrazones as a rule undergo slow decomposition when dried in air. In general, when derivatives of phenylhydrazine are involved, it is recommended that the product be crystallized immediately and dried as rapidly as possible for melting-point determination.

A number of carbonyl compounds fail to give stable phenylhydrazones even when the derivatives are prepared from pure reagents and with the utmost care. For example, cyclohexanone and acetophenone yield derivatives that melt 5–10° below the melting point of the pure compounds; even after crystallization the derivatives undergo change in the melting point when dried in a desiccator.

The preparation of nitrosubstituted phenylhydrazones, particularly the *2,4-dinitrophenylhydrazones,* is advisable for semimicroquantities. In most cases it is possible to start with as little as 20–30 mg of the carbonyl compound and obtain a sufficient quantity of the pure derivative for several determinations of the melting point. For the preparation of the 2,4-dinitrophenylhydrazones, the carbonyl compound and a small amount of hydrochloric acid are added to a hot saturated alcoholic solution of 2,4-dinitrophenylhydrazine. The derivative that separates out on cooling in many cases does not require further purification. In some cases the use of nitrosubstituted phenylhydrazones may be limited by the high melting points of the derivatives; in such instances the use of phenylhydrazones may be found suitable. For example, the 2,4-dinitrophenylhydrazone of piperonal melts at 266°, whereas the semicarbazone of the same aldehyde melts at 234°; in this case the derivative with phenyl-

hydrazine melting at 102° is preferable, since it may be prepared easily and is relatively stable. Another limitation of the 2,4-dinitrophenylhydrazones is that they are not very satisfactory for α-hydroxyaldehydes, ketones, and sugars; on the other hand, ethylacetoacetate gives a derivative readily.

Equation (4) represents the formation of a *semicarbazone*. Generally carbonyl compounds react rapidly with semicarbazide to yield crystalline derivatives, so that in many cases the separation of crystals begins upon warming the reaction mixture. This fact should not be taken as evidence that all carbonyl compounds react readily with semicarbazide for, with the lower aldehydes, the time required for complete reaction is several days. For example, a mixture of formaldehyde and semicarbazide does not yield a crystalline derivative even after 10 days; if sodium acetate is omitted from the reaction mixture, an amorphous polycondensation product of formaldehyde and semicarbazide is formed. Acetaldehyde forms slowly a soluble semicarbazone that is not easily isolated. Complications may also arise on prolonged standing or heating in order to complete the reaction, such as the formation of acetylsemicarbazones and hydrazodicarbonamides. Therefore, it is advisable not to attempt the preparation of semicarbazones of aldehydes with less than 5 carbon atoms. Most ketones yield semicarbazones quite readily; acetone requires heating for about 1 hour for complete reaction.

Thiosemicarbazide is a valuable reagent for the preparation of derivatives of semimicroquantities of the lower aldehydes and ketones, particularly in the presence of alcohols. Since it is approximately 10 times as costly as semicarbazide, its use is indicated only when other derivatives are found unsuitable. Directions for the preparation of thiosemicarbazide are given in Section 11.10, page 249.

Among other substituted semicarbazides that have been proposed for the characterization of aldehydes and ketones are: *o*, *m*, and *p-tolylsemicarbazones; phenylsemicarbazones, 3,5-dinitrophenylsemicarbazones; α-*, and *β-naphthylsemicarbazones;* and *xenylsemicarbazones.*

Equation (5) represents the formation of an *oxime;* most of the oximes of the lower aldehydes and ketones are of little value with semimicroquantities. The reaction between hydroxylamine and the carbonyl compounds requires in many cases several hours and in the lower aldehydes several days to reach completion; further, the melting points of a large number of oximes is below 70°, and, as a result, crystallization, separation, and purification are difficult. In the preparation of oximes it is advisable to use 500 mg of the carbonyl compound for the reason that,

owing to the difficulties in formation, separation, and purification, the yields are generally poor.

Equation (6) represents the reaction of an aldehyde with dimethylcyclohexanedione, commonly known as "*methone*" reagent; the compound is also called in the literature dimethyldihydroresorcinol. One mole of the aldehyde condenses with two moles of the reagent, and therefore the derivatives are often named with prefix of the aldehyde and the ending *dimethone*—for example, *formaldimethone* and *acetaldimethone*. The reaction is not given by ketones and is helpful for detecting traces of the aldehydes. The bromo-substituted (dibromomethone) reagent is very useful in spot-plate tests for the detection of microquantities of aldehydes.

The methone derivatives of most aldehydes can be made to undergo cyclization to give octahydroxanthenes. The usual method is to heat the methone derivative with acetic anhydride or with alcohol containing a small amount of hydrochloric acid. The cyclization usually requires five minutes, and the yield is nearly quantitative. In most cases the melting points of the new derivatives (octahydroxanthenes) differ by more than 15° from those of the methones; therefore it is possible to prepare two different derivatives through the reaction. The methone is first prepared, and after the determination of the melting point it is then converted by cyclization to the xanthene derivative.

In the cases of the higher aldehydes and methyl ketones, derivatives may be obtained by oxidation to carboxylic acids. The oxidation of *m*-nitrobenzaldehyde to *m*-nitrobenzoic acid, shown in Equation (7) and described on page 174, is an example of the oxidation of aldehydes for characterization purposes. Although the oxidation of ketones to carboxylic acids is more involved, it is possible in the case of methyl ketones to remove the methyl group by means of oxidation with sodium hypochlorite (haloform reaction). This reaction is particularly useful in the case of unsaturated methyl ketones, since the double bond is not attacked.

Among other derivatives that have been proposed for the characterization of carbonyl compounds the following are mentioned: (a) *benzothiazolines* formed by the reaction of carbonyl compounds and 2-amino-4-chlorothiophenol; (b) substituted *hydantoins* formed by the reaction of a dilute alcoholic solution of the carbonyl compound with potassium cyanide and ammonium carbonate; and (c) *benzylideneaminomorpholine* compounds formed by the reaction of aldehydes with 4-aminomorpholine. The preparation of hydantoins is of interest since the reagents are inex-

pensive, easily available, and the derivatives of many carbonyl compounds are readily formed in a state of high purity.

11.1 Butanone semicarbazone. Place in an 8-inch tube 200 mg of semicarbazide hydrochloride, 300 mg of sodium acetate, and 2 ml of water. Warm for a few seconds over a small flame to effect solution. Add 0.2 ml of butanone with a pipette or a dropper. Stopper with a cork provided with a reflux condenser, place tube in a beaker containing water at 70–75°, and heat at this temperature for 10 minutes. Allow the tube to remain in the water bath for 10 additional minutes. Filter and wash crystals with 5 drops of cold water. Keep about 5 mg of the crystals and recrystallize the main portion from 1.5 to 2 ml of water. The yield is 60–70 mg, melting at 135–6°.

Note: For acetone, it is advisable to heat at 50° for about 1 hour; otherwise the yield is poor. For the higher aliphatic ketones, use 2 ml of methanol and 2 ml of water as a solvent for the reaction mixture. Since the solubilities of the semicarbazones decrease with increase in the complexity of the molecule, good results are obtained by using 100 mg of the carbonyl compound. Thus, 2-heptanone (methyl-*n*-hexyl ketone) and cyclohexanone give about 100 mg of pure derivative from 0.1 ml of the compound. Aromatic ketones react slower and a longer period of heating the reaction mixture is recommended.

11.2 Benzaldehyde semicarbazone. Place in an 8-inch tube 100 mg of semicarbazide hydrochloride, 150 mg of sodium acetate, 1 ml of water, and 1 ml of alcohol. Add 0.1 ml of benzaldehyde and heat tube in a water bath at 70° for 10 minutes. Add 2 ml of water and cool. Filter the crystals and wash with two 1-ml portions of water. Recrystallize from a mixture of 6 ml of methanol and 2 ml of water. The yield is 80 mg, melting at 221–222°.

Note: The semicarbazones of aromatic aldehydes have melting points usually above 200° and care must be taken to apply proper thermometer corrections.

11.3 Piperonal phenylhydrazone. Place in an 8-inch tube 200 mg of piperonal and 5 ml of methanol. Heat for a few seconds to effect solution; then add 0.1 ml of phenylhydrazine. (**Caution:** *Use care in handling the reagent.*) Boil the mixture for 1 minute and add 1 drop of glacial acetic acid and boil gently for 3 minutes. Add dropwise 1.5 ml of water until a permanent cloudiness results. Cool, filter the crystals, and wash with 1 ml of water containing 1 drop of acetic acid. Recrystallize the product immediately by dissolving it in 3 ml of hot methanol. Add 0.5 ml of water to the hot solution, cool, and scratch the sides of the tube, if crystals do not separate readily. Filter, wash with a few drops of 50

per cent methanol, and dry rapidly by pressing the crystals first between filter paper before spreading on the paper filter disc. Determine the melting point as soon as the crystals are dry. The yield is about 80–100 mg of the product, melting at 99–100°.

Note: Other aromatic aldehydes, such as *vanillin* and *m-nitrobenzaldehyde*, yield phenylhydrazones readily by the same method as described for piperonal.

11.4 Benzophenone phenylhydrazone. The same quantities and reagents are used as above. The mixture, however, is heated for 15 minutes. The product is crystallized from 10 ml of methanol. It may require 2 crystallizations for complete purification. The yield of phenylhydrazone is about 90–100 mg, melting at 136–137°.

Note: A number of ketones, such as *acetophenone* and *cyclohexanone*, react anomalously with phenylhydrazine. For example, following the same method as outlined, acetophenone yields a product that shows an initial melting point of 98°, which is 7° below the melting point of the pure derivative. Even after crystallization, the product undergoes decomposition when dried in air.

11.5 Benzaldehyde p-nitrophenylhydrazone. Place in an 8-inch tube 8 ml of methanol and 50 mg of *p*-nitrophenylhydrazine; heat until solution is complete. Add 0.2 ml of benzaldehyde and boil for 1 minute; add one drop of glacial acetic acid and then boil gently for 4–5 minutes. Then add water dropwise until a faint cloudiness results. Heat until the solution becomes clear and then cool. Filter crystals and wash with 3–4 ml water containing 2 drops of acetic acid. Crystallize the product by dissolving in 7–10 ml·of methanol and adding 1–1.5 ml of water to the hot solution. The yield is 80–100 mg of crystals, melting at 190°.

11.6 Formaldehyde 2,4-dinitrophenylhydrazone. Place in an 8-inch tube 10 ml of methanol and 40 mg of 2,4-dinitrophenylhydrazine. Boil for a few minutes under reflux to effect solution. If all the solid does not dissolve, remove the flame and, after 1 minute, pour the clear solution into another test tube. Add to the clear solution 0.4 ml of 40 per cent aqueous formaldehyde solution and boil for 1 minute; add 2 drops of 6 *N* hydrochloric acid solution (or 1 drop of concentrated acid) and boil gently for 1–2 minutes. Add about 1–2 ml of water and cool. Filter the crystals and recrystallize from a mixture of 3 ml of methanol and 1 ml of water. The yield is about 20 mg of crystals, melting at 166–7°.

11.7 Acetone 2,4-dinitrophenylhydrazone. Proceed by the same general method as described above in Section 11.6, and use 0.2 ml of acetone. The yield is about 50 mg, melting at 126°. If it is desired to recrystallize the derivative, use 3–4 ml of methanol and add water to the hot alcohol solution until a cloudiness results.

Note: For aromatic aldehydes and ketones, the amount of the materials (carbonyl compound, solvent, and reagent) may be reduced to one half. When 50 mg of *benzaldehyde* are used, 20 mg of the pure derivative are obtained after crystallization from 4 ml of methanol; *o-chlorobenzaldehyde* yields 25 mg of the pure derivative.

11.8 Methone derivative of butanal. Place in a test tube 300 mg of methone, 3 ml of a 50 per cent methanol-water mixture, 50 mg of butanal and 1 drop of piperidine. Heat in a water bath under reflux for 10 minutes. If the solution is clear at this point, add water dropwise until a cloudiness appears, then cool the mixture. Filter and wash the crystals with two 1-ml portions of 30 per cent methanol. The crystals melt at 134–135°; the yield is 120–130 mg. If crystallization is necessary, the solid is dissolved in 1 ml of methanol and water is added dropwise until a permanent cloudiness results; the solution is warmed until clear and then cooled. About 60 mg of the methone derivative are obtained and additional amounts of crystals separate out from the filtrate on standing.

Note: The preparation of methone derivatives is recommended when only a small amount of the aldehyde is available. For example, 1 drop of butanal is added to a solution of 50 mg of methone, dissolved in 0.5 ml of methanol, in a small test tube and allowed to stand for 4 hours. A sufficient amount of the derivative is obtained for several determinations of the melting point. The methone derivatives separate out slowly from solutions; a cloudy filtrate is an indication that crystallization is incomplete; in such cases the mixture is corked and allowed to stand in the cold overnight. For the cyclization of the methone derivative, 50 to 100 mg of the crystals are dissolved in 2–4 ml of a hot 80 per cent methanol-water mixture; one drop of concentrated hydrochloric acid solution is added and the solution is heated under reflux for five minutes. Water is added dropwise until a cloudiness appears. The xanthene derivative separates out on cooling. The values of the melting points of the xanthene derivatives do not appear on the tables of this text, but can be found by consulting the original article cited in the bibliography section.

11.9 General method for oximes. Place in an 8-inch test tube 500 mg of the aldehyde or ketone, 500 mg of hydroxylamine hydrochloride, 3 ml of pyridine and 3 ml of absolute alcohol. Arrange for reflux and boil the mixture gently for 2 hours on a steam bath. Pour the mixture in an evaporating dish and remove the solvent in a current of air under a hood. Scrape the residue by means of the microspatula and grind with 3 ml of cold water; filter and recrystallize the oxime from methanol, or methanol-water mixture.

Note: In the preparation of some oximes, the pyridine may be replaced with 4 ml of 1 N sodium hydroxide solution, and absolute alcohol with ordinary

methanol. The mixture is heated for 10–20 minutes and then cooled in an ice-salt mixture.

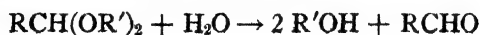
11.10 Preparation of thiosemicarbazide. Prepare a solution of 5 g hydrazine sulfate and 2.7 g anhydrous potassium carbonate in 20 ml of hot water; add to this mixture 4 g of potassium thiocyanate and boil for a few minutes. Remove the vessel from the flame and after a minute or two add 25 ml of hot ethanol; a white precipitate of potassium sulfate separates out and is filtered with suction. The solid is washed with 5 ml of hot ethanol and the washings are united with the filtrate. Evaporate the alcohol from the filtrate over the steam bath and boil the solution in a small casserole until the volume is about 3–4 ml and very syrupy. Cool the mass for several hours. Filter the crude semicarbazide with suction. The yield of the crude semicarbazide is 500–900 mg; a considerable amount of thiosemicarbazide remains in the syrupy filtrate and may be used directly for the preparation of thiosemicarbazones, as illustrated in section 11.11. If no solid separates out from the syrupy liquid and it is desired to separate the pure compound, add a few drops of concentrated hydrochloric acid; the hydrochloride of thiosemicarbazide separates out and is filtered with suction. Both semicarbazide and its hydrochloride may be crystallized from hot water. Thiosemicarbazide melts at 181–183° and the hydrochloride at 186–190°.

11.11 Acetone thiosemicarbazone. In a 6-inch test tube place 0.5 ml of the syrupy liquid from preparation 11.10 (or 50 mg of pure thiosemicarbazide) and add 2 drops of acetone (about 50 mg). Place in a separate tube 100 mg of sodium acetate and 1 ml of water; heat until the sodium acetate dissolves and add the solution to the mixture of acetone and thiosemicarbazide. Warm for a minute and set aside. The thiosemicarbazone begins to separate immediately. After 15 minutes cool and filter with suction, washing with 0.5 ml of water. About 25–30 mg of fine crystals are obtained, which melt at 177–8°.

Note: For the preparation of the thiosemicarbazones of citral and citronellal and other carbonyl compounds not readily soluble in water a small amount of alcohol is added, and the tube is then heated in a water bath for 15–30 minutes at 60–70°.

Derivatives of Acetals

The acetals are included under the carbonyl compounds since on hydrolysis they yield aldehydes and alcohols:

$$RCH(OR')_2 + H_2O \rightarrow 2\,R'OH + RCHO$$

The hydrolysis is best accomplished by heating with dilute acids; the lower acetals are usually hydrolyzed by boiling with 3–5 per cent hydrochloric or sulfuric acid; for the hydrolysis of the higher acetals an organic solvent miscible with water and heating for 20–30 minutes or longer is necessary. One method is to use a 50 per cent solution of dioxane and water and, after the hydrolysis is complete, to neutralize the hydrolysate and divide in half; one portion is used for the characterization of the aldehyde and the second portion for the derivitization of the alcohol. For semimicroquantities it is often more convenient to hydrolyse 100–200 mg quantities of the acetal separately for each characterization. This procedure is outlined in detail in the following section dealing with the hydrolysis of the dimethylacetal of benzaldehyde, a commercial product used in perfumery. In general, however, the hydrolysis of the acetal and subsequent preparation of the derivatives for the alcohol and the aldehyde depend on the nature of the compound and the hydrolysis products. The methods for the preparation of the derivatives are to be found in the sections dealing with the alcohols and carbonyl compounds.

11.12 Hydrolysis of benzaldehyde dimethyl acetal: a. *Identification of the aldehyde.* Place in an 8-inch tube 100 mg (4–5 drops) of the acetal, 0.5 ml (10 drops) of 6 *N* sulfuric acid, 2 ml of water, and 2 ml of ethanol. Arrange for reflux and boil the mixture gently for 5 minutes. Add 100 mg of semicarbazide hydrochloride and a drop of Universal indicator and then dropwise 6 *N* sodium hydroxide solution to *p*H 5; add 200 mg of sodium acetate and shake to dissolve the solid. The semicarbazone separates immediately. Cool for a few minutes and then filter; wash the solid with water and then transfer it back to the 8-inch tube from which it was filtered. Add 2.5–3 ml of methanol, heat to boiling, and filter; add to the hot filtrate 0.5 ml of water and cool for 5 minutes. Filter the crystals of the semicarbazone of benzaldehyde and dry. The yield is 70–90 mg.

b. *Identification of the alcohol.* Place in an 8-inch distilling tube 200–300 mg of the acetal, 0.5 ml of 6 *N* hydrochloric acid solution, 2.5 ml of water, and 2.5 ml of dioxane. Insert in the mouth of the tube a cork holding a reflux condenser that protrudes into the tube at least 25 mm below the side arm. Connect the end of the side arm with a delivery tube into an arrangement for regular distillation. Add a boiling stone and reflux for 15 minutes. Pull the condenser upwards until the tip is just above the side-arm opening and continue the gentle boiling so that distillation proceeds slowly. When 3 ml of distillate have been collected, discontinue the distillation. Treat the distillate according to Procedure 10.1, page 226, using proportionate amounts. Since the maximum

amount of methanol resulting from the hydrolysis is about 125 mg, the amounts of reagents should be based on this quantity.

Caution. Where appreciable amounts of acetals are involved, the reader should bear in mind that these compounds form peroxides like the ethers, and therefore the precautions outlined on page 236 should be followed.

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Derivatives of Primary and Secondary Amines

When primary and secondary amines react with acyl and aroyl halides, substituted amides are formed; the reaction of amines with isocyanates and isothiocyanates yields substituted ureas and thioureas. These reactions are important in the preparation of derivatives for the characterization of primary and secondary amines. They are exemplified by the following equations:

$$C_6H_4(Br)NH_2 + (CH_3CO)_2O \longrightarrow CH_3CONHC_6H_4(Br) + CH_3COOH \quad (1)$$

p-Bromoaniline; Acetic anhydride; N-*p*-Bromophenylacetamide (*p* Bromoacetanilide)

$$C_2H_5NH_2 + C_6H_5COCl \longrightarrow C_6H_5CONHC_2H_5 + HCl \quad (2)$$

Ethylamine; Benzoyl chloride; N-Ethylbenzamide

$$C_6H_5NH_2 + 2\,C_6H_5SO_2Cl \longrightarrow C_6H_5SO_2NHC_6H_5 + HCl \quad (3)$$

Aniline; N-Phenylbenzenesulfonamide

$$C_6H_5NHCH_3 + 2\,C_6H_5SO_2Cl \longrightarrow C_6H_5SO_2N(CH_3)C_6H_5 + HCl \quad (4)$$

Methylaniline; N-Phenylmethylbenzenesulfonamide

$$(CH_3)_2NH + CH_3C_6H_4SO_2Cl \longrightarrow CH_3C_6H_4SO_2N(CH_3)_2 + HCl \quad (5)$$

Dimethylamine; *p*-Toluenesulfonchloride; N-Dimethyl-*p*-toluenesulfonamide

$$CH_3(CH_2)_4NH_2 + C_6H_5NCS \longrightarrow C_6H_5NHCSNH(CH_2)_4CH_3 \quad (6)$$

n-Amylamine; Phenylisothiocyanate; *sym*-*n*-Amylphenylthiourea

$$(C_4H_9)_2NH + C_6H_5NCS \longrightarrow C_6H_5NHCSN(C_4H_9)_2 \quad (7)$$

Di-*n*-butylamine; *sym*-Phenyl-di-*n*-butylthiourea

$$C_6H_5NH_2 + C_{10}H_7NCO \longrightarrow C_6H_5NHCONHC_{10}H_7 \quad (8)$$

Aniline; α-Naphthylisocyanate; *sym* Phenyl-α-naphthylurea

(9)

RNH_2 or R_2NH + 3-Nitrophthalic anhydride (NO_2-substituted ring with CO–O–CO) ⟶ N-Substituted 3-Nitrophthalamic acid (ring with COOH, CONHR, NO_2) $\xrightarrow{-H_2O}$ 3-Nitrophthalimide (ring with CO–NR–CO, NO_2)

⟶ N,N-Disubstituted Nitrophthalamic acid (ring with COOH, $CONR_2$, NO_2)

$$(NO_2)_2C_6H_3COOH + CH_3NH_2 \longrightarrow (NO_2)_2C_6H_3COOH_3NCH_3 \quad (10)$$

3, 5-dinitrobenzoic acid; Methylammonium-3,5-dinitrobenzoate

Equation (1) represents the use of acetic anhydride for the *acetylation* of amines. Generally, acetylation is useful with arylamines, but the acetylalkylamines (amides) have on the whole low melting points. The usual method of acetylation is to heat the amine with a slight excess of acetic anhydride and then separate the substituted amide by adding water. In a few cases acetic anhydride may be used for acylations like benzoyl chloride and under similar conditions—namely, in the cold in alkaline solution. Difficulties are encountered in the acetylation of substituted arylamines, particularly when the substituent is in the *ortho* position with respect to the amino group. The substituent may exert a retarding effect on the acetylation or an accelerating effect, which gives rise to considerable amounts of diacetyl derivatives. The retarding effect is illustrated by a comparison of the acetylation of *o*-nitroaniline and *p*-nitroaniline; 100 mg of the base, 300 mg of acetic anhydride, and 2 ml of pyridine were boiled for 60 minutes. About 100 mg of the acetyl derivative of *p*-nitroaniline were isolated; from the acetylated mixture of *o*-nitroaniline a product was isolated melting 4° below the melting point of the pure amine, indicating that very little acetylation took place. This behavior may be ascribed to chelation and to proton repulsion by the nitro group, which produce a lowering in the basicity of the amine; the effect is greater in *o*-nitroaniline, as shown by its basic ionization constant, 10^{-14}, as compared with 10^{-12} for *p*-nitroaniline. The accelerating effect in acylation is illustrated by the acetylation of α-naphthylamine. Heating of 100 mg of α-naphthylamine with 300 mg of acetic anhydride for 3–5 minutes gives a product that melts, after 1 crystallization, at 142°, whereas heating for 10 minutes gives a product melting at 128°. Although the diacetyl derivative may be hydrolyzed, such a procedure is not recommended unless another suitable derivative cannot be prepared easily.

Equation (2) represents the formation of a substituted *benzamide* by reacting the amine with benzoyl chloride. The best procedure for benzoylation is to suspend the amine in an aqueous alkaline solution and add the aroyl chloride in small amounts with vigorous shaking, keeping the mixture cold; this method is often called the *Schotten-Baumann method* or *reaction.* On the whole, the preparation of substituted benzamides is satisfactory; it is recommended that beginners consider the preparation of substituted benzamides if their melting points are above 60°. *p*-Nitrobenzoyl chloride and 3,5-dinitrobenzoyl chloride react in the same manner as benzoyl chloride; the melting points of the nitrosubstituted benzamides are as a rule above 200° and hence are not recommended as a first choice. Further, since the chlorides are solid, heating in presence of

pyridine is necessary in most cases. The N-substituted 3,5-dinitrobenzamides should not be confused with the 3,5-dinitrobenzoates; the latter are salts formed by the reaction of 3,5-dinitrobenzoic acid with the amines.

Equations (3), (4), and (5) represent the formation of various *substituted sulfonamides.* The benzenesulfonamides are among the most commonly prepared derivatives for primary and secondary arylamines. Of particular interest is the fact that many of the N-substituted sulfonamides of the primary amines, $C_6H_5SO_2NHR$, are soluble in alkali. The solubility is assumed to be due to the proximity of the strongly polar sulfonic acid group, which exerts a repulsion on the hydrogen atom attached to the amino nitrogen; as a consequence, these compounds form soluble alkali salts, of the type $(C_6H_5SO_2NR)^-Na^+$. It should be remarked, however, that not all N-substituted sulfonamides of the primary amines are soluble in alkali. The sulfonamides of primary amines of the type $C_6H_5(CH_2)_3NH_2$ are not soluble in alkali; further, the separation of N-substituted sulfonamides from N,N-disubstituted sulfonamides is not so complete as it is represented by general equations. For example, when a mixture of aniline and methylaniline is treated with benzenesulfonyl chloride in presence of 10 per cent sodium hydroxide solution, the N-phenylbenzenesulfonamide and the N,N-methylphenylbenzenesulfonamide that are separated require 3–4 crystallizations for purification. Many substituted benzenesulfonamides have been described in the literature as suitable derivatives for amines; the following partial list is arranged in decreasing order of utility for semimicro work: *p-toluenesulfonamides*, *m-nitrobenzenesulfonamides*, *p-bromobenzylsulfonamides*, and *methanesulfonamides.*

Equations (6), (7), and (8) represent the formation of *substituted ureas* and *thioureas* by reaction of amines with isocyanates and isothiocyanates. The preparation of thioureas is preferable to that of ureas because the isothiocyanates do not react so easily with moisture as the isocyanates. Because of the lower rates of reaction, isothiocyanates may be used in presence of alcohols. The mixture of amine and isothiocyanate dissolved in alcohol is heated for a short time; on cooling and careful addition of water, the thioureas separate, usually as oils, which on standing crystallize as well-defined solids. The tendency of thioureas to separate as oils from concentrated alcoholic or aqueous-alcoholic solutions is particularly marked in the case of alkylamines. However, when all factors are considered, the thioureas are often the most suitable derivatives for many of the alkylamines. α-Naphthylisothiocyanate may be used in place of phenylisothiocyanate if a thiourea with a higher melting point is

desirable. Among other isothiocyanates that have been proposed in the literature for the preparation of thioureas are: *o-* and *p-tolyl, p-chlorophenyl, p-xenyl, m-nitrophenyl,* and *α-* and *β-naphthyl.* The following isocyanates and substituted azides may be used for the preparation of substituted ureas: *α-* and *β-naphthyl, m-* and *p-nitrophenyl, 3,5-dinitrophenyl, m-* and *p-chlorophenyl,* and *m-* and *p-bromophenyl.*

Equation (9) represents the use of 3-nitrophthalic anhydride for the preparation of derivatives and separation of primary and secondary amines. As shown by the equations, primary amines form *N-substituted 3-nitrophthalamic acids*, which, when heated to 145°, are converted to *substituted 3-nitrophthalimides;* secondary amines form *N,N-disubstituted nitrophthalamic acids*, which are stable to heat. A mixture containing derivatives from primary and secondary amines may be separated by the addition of sodium bicarbonate solution, which dissolves the latter but not the former. The use of 3-nitrophthalic anhydride is indicated in connection with amines, such as *o*-nitroaniline, which fail to give derivatives by the usual methods.

Equation (10) represents the use of a carboxylic acid for the preparation of salts of amines; the amine salts are used for characterization through determination of the melting point. Other acids that have been recommended for the preparation of amine salts are: 2,4-dinitrobenzoic acid, *p*-toluenesulfonic acid, *m*-nitrobenzenesulfonic acid, and other benzene, naphthalene, and anthraquinone sulfonic acids, which are listed in the Bibliography (pages 266–7).

Among other derivatives proposed for the characterization of primary and secondary amines are the following: (a) substituted *2-isonitrosocyclohexane* derivatives formed by the reaction of amines with *1-(2-isonitrosocyclohexyl)pyridinium chloride;* (b) *picramides* formed by reaction of the amines with *picryl chloride;* (c) *sulfone-bis-acetamides* formed by the reaction of esters of *sulfone-bis-acetic acid* with amines; (d) *2-nitrobenzenesulfenamides* and *2,4-dinitrobenzenesulfenamides* formed by the reaction of the amines with the corresponding *sulfenyl chlorides;* and (e) *salts* of the amines with *arylsulfonic acids.*

Derivatives of Hydrazines

Phenylhydrazine, $C_6H_5NHNH_2$, and its substituted derivatives are the most common hydrazines; these compounds for the most part are strongly basic, dissolve in dilute hydrochloric acid, forming salts, and reduce Fehling's solution; they are also easily reduced to ammonia and a primary arylamine, as, for example, in the formation of the osazones of

the carbohydrates. The derivatives most suitable for their characterization are the hydrazones with the carbonyl compounds; these derivatives are not listed in the table on amines but can be found in the tables of carbonyl compounds. For example, the derivatives listed for phenylhydrazine are benzenesulfonamide, acetamide, benzamide, and the like; however, it is more convenient to identify phenylhydrazine by the condensation with an aldehyde, as, for example, benzaldehyde, to obtain the phenylhydrazone.

11.13 Aceto-o-bromoanilide (N-*o*-bromophenylacetamide). Place in an 8-inch tube 100 mg of *o*-bromoaniline and 0.3 ml of acetic anhydride. Provide the tube with a micro reflux condenser and heat for 5 minutes by means of a small flame so that the mixture boils gently. The condenser may be omitted if the flame is so adjusted that the vapors of the mixture rise to about the middle of the tube. Cool and add 3 ml of water. Heat for a few minutes to dislodge the mass of crystals from the bottom of the tube and then cool and filter the crystals; wash once with 3 ml of 10 per cent hydrochloric acid solution and twice with 2 ml of water. Recrystallize by dissolving the solid in 8 ml of methanol and adding 3 ml of water to the hot, filtered solution. Cool, filter the solid, and wash twice with 3 ml of water. The yield is 100–120 mg of crystals, melting at 98–9°.

Note: The acetyl derivatives may at times separate as oils when water is first added to the reaction mixture; the oils usually solidify, however, when the mixture is vigorously stirred and rubbed against the sides of the tube. When stirring and scratching fail to induce crystallization, cautiously add dilute sodium hydroxide solution to neutralize part of the acetic acid formed by the hydrolysis of the anhydride.

When the acetyl derivative is formed at a slow rate, as in the case of amines that have low basicity, the reaction mixture is heated for 0.5-1 hour in presence of anhydrous benzene or pyridine. Since the latter solvent is a proton-acceptor, it is the more suitable; this is illustrated by the acetylation of *p*-nitroaniline.

As previously mentioned, diacetylation occurs to some extent with primary amines. In general, it is advisable for beginners to undertake the preparation of other derivatives if acetylation proves unsatisfactory. References to the literature regarding diacetylation of amines are given in the Bibliography Section.

11.14 Aceto-p-nitroanilide (*N-p-nitrophenylacetamide*). Place in an 8-inch tube 100 mg of *p*-nitroaniline, 0.3 ml of acetic anhydride, and 2 ml of pyridine. Provide the tube with a micro reflux condenser and adjust the flame so that the mixture boils gently. Heat for 0.5 hour and then cool; add 10 ml of 2 per cent sulfuric acid solution and shake the

tube so as to mix the contents thoroughly. Cool in running water for 10 minutes. Filter the solid and wash twice with 2 ml of 2 per cent sulfuric acid. Dissolve the crystals in 6 ml of methanol, filter, and add 3 ml of water. Cool for 10–15 minutes and then filter; wash twice with 1 ml of 50 per cent methanol. The yield is 110–130 mg, melting at 214–215°.

11.15 N-Ethylbenzamide. In an 8-inch tube, provided with a solid rubber stopper, place 0.4 ml of an aqueous (33 per cent) solution of ethylamine; add, by means of a pipette dropper, 0.6 ml of benzoyl chloride and then 6 ml of 10 per cent solution of sodium hydroxide. Stopper the tube and shake for 1 minute, then at intervals over a period of about 5 minutes. After each shaking, release carefully the rubber stopper (*preferably in a hood, since the vapors of benzoyl chloride have lacrymatory properties*). The oil that separates at first soon crystallizes in shiny plates. Cool and filter the crystals; wash twice with water. Neutralize the filtrate cautiously to about *p*H 7–8 in order to precipitate an additional amount of the derivative dissolved by the excess of alkali. Dissolve the combined solid in 1–2 ml of boiling methanol and filter; wash the tube with 0.5 ml methanol and add the washings to the filtrate. To the filtrate add 3 ml of water and cool for 30 minutes. If crystals do not separate within 5 minutes, scratch the inner side of the tube by means of a glass rod. Filter and wash twice with 1 ml of water. The yield is 40–50 mg, melting at 70–71°.

Note: The benzoyl derivatives of the primary amines have a tendency to dissolve in excess of alkali; it is advisable, therefore, to neutralize the filtrate with dilute hydrochloric acid. It is evident, however, that the precipitated derivative from the filtrate will contain a small amount of benzoic acid resulting from the hydrolysis of the reagent; the amount of benzoic acid which is coprecipitated can be kept to a minimum if on neutralizing with dilute acid the *p*H is adjusted (with the aid of Universal indicator) to about 8.

11.16 N-Cyclohexylbenzamide. Place into an 8-inch test tube 100 mg of cyclohexylamine and 0.3 ml of benzoyl chloride. Cool in tap water and add 3 ml of 10 per cent sodium hydroxide solution. Stopper the tube by means of a solid rubber stopper and shake vigorously for 1 minute; crystals separate immediately. Allow to stand for 5 minutes with occasional shaking; then filter and purify as in Section 11.15 above. Use 3–4 ml of methanol for solution of the solid; filter, and add 1 ml of hot water to the filtrate. The yield is 90–100 mg, melting at 148–149°.

11.17 N-o-Tolylbenzamide. Use 0.1 ml of *o*-toluidine, 0.5 ml of benzoyl chloride, and 6 ml of sodium hydroxide solution and proceed as

in Section 11.15. Dissolve the derivative in 10 ml of hot methanol and add 1 ml of water to the filtered hot solution. The yield is about 120 mg, melting at 142–143°.

Note: *Ethyl-p-aminobenzoate* and *anthranalic acid* are benzoylated easily by the same method. The reaction mixture, however, should be cautiously neutralized with dilute hydrochloric acid in order to precipitate completely the derivative. From 100 mg of *ethyl-p-aminobenzoate*, 120–130 mg of pure benzoyl derivative are obtained, having a melting point of 147–8°; similarly, 100 mg of *anthranilic* acid yield 110–120 mg of the benzoyl derivative, melting at 180–181°.

11.18 N-Phenylbenzenesulfonamide. Place in an 8-inch test tube 0.1 ml of aniline, 0.2 ml of benzenesulfonyl chloride, and 5 ml of 10 per cent sodium hydroxide solution. Stopper the tube by means of a solid rubber stopper and shake at frequent intervals for 3 minutes. Remove the stopper and warm the tube; then shake again for 1 minute. Cool in running water and then add carefully dilute hydrochloric acid solution to neutralize the excess of sodium hydroxide. Filter the crystals and wash twice with 3 ml of water. Dissolve the derivative in 8 ml of hot methanol, filter, and add 3 ml of water to the filtrate. The product melts at 109–110° and requires an additional recrystallization to give a melting point of 111–112°. The yield of the pure sulfonamide is about 140–150 mg.

11.19 Separation of the benzenesulfonyl derivatives of aniline and methylaniline. Place in an 8-inch test tube 0.1 ml of aniline, 0.1 ml of methylaniline, and 0.4 ml of benzenesulfonyl chloride. Add 8 ml of 10 per cent sodium hydroxide solution and shake at frequent intervals over a period of 3–4 minutes. Allow to stand for 10 minutes with occasional shaking. Warm to remove any excess of sulfonyl chloride; then cool. Filter and wash crystals with 3 ml of water. Place the filtrate aside and transfer the crystals into a test tube; add 5 ml of 2 per cent sodium hydroxide solution and warm to about 50°. Place a solid rubber stopper into the mouth of the tube and then shake the contents vigorously for about 1 minute. Allow the mixture to stand for 2–3 minutes, but at intervals shake the tube vigorously. Cool and filter the crystals. Combine the filtrates with those previously obtained and which contain the benzenesulfonyl derivative of aniline in solution. Wash the crystals of the methylamine derivative with 2–3 ml of water. Transfer the solid into a test tube and dissolve it in 5–6 ml of hot methanol; filter and add 1 ml of water to the hot solution. Cool and filter the crystals. The yield is 150 mg of crystals, melting at 78–79°.

The combined filtrates containing the derivative of aniline in solution are carefully neutralized with dilute hydrochloric acid. The precipitated crystals are filtered and washed 3 times with 3 ml of water, then transferred into a test tube and suspended in 5 ml of water. Sodium hydroxide solution (10 per cent) is added dropwise, the tube being shaken after the addition of 2–3 drops, until an opalescent solution results. A minute amount of charcoal is added and the solution filtered. The substituted sulfonamide is precipitated by the addition of dilute hydrochloric acid, filtered, and then crystallized as in Section 11.18 above. The yield is 90–100 mg of crystals, melting at 111°.

Note: The above procedure (often called *Hinsberg's method*) may be used for the separation of primary, secondary, and tertiary amines. If any tertiary amine is present, the reaction mixture is acidified with dilute acid and the precipitated sulfonamides are filtered off and washed with a 10 per cent solution of hydrochloric acid. Any tertiary amine originally present is removed. The mixed sulfonamides are then separated by treatment with dilute alkali. The arylsulfonyl derivatives of primary and secondary amines are usually contaminated with disulfonyl derivatives formed by such reactions. Such disulfonyl derivatives are often insoluble in dilute alkali and are a source of contamination to the arylsulfonyl derivatives of secondary amines. When the melting point of such arylsulfonyl derivative varies more than 5° from the melting point listed in the literature, the crystals are refluxed for 10–15 minutes with a solution of sodium methoxide, prepared by dissolving 0.5 g of sodium in 10 ml of methanol. By this treatment the disulfonyl derivative is hydrolyzed to the mono-derivative. The mixture is evaporated almost to dryness and then diluted with 10 ml of water; the crystals are filtered and purified.

The separation of the benzenesulfonyl derivative, by means of solubility in alkali, of compounds that possess an amino hydrogen atom is not applicable to all classes of amines. As the solubility of the alkylamines decreases, the sodium salts of the benzenesulfonyl ($RN(Na)(SO_2C_6H_5)$) become insoluble; therefore, the method is not satisfactory with alicyclic amines and the higher alkylamines.

11.20 N-Butyl-p-bromobenzenesulfonamide. Place in an 8-inch test tube 100 mg of *p*-bromobenzenesulfonyl chloride and 70 mg (3 drops) of *n*-butylamine. Warm the tube by means of a small flame until the solid chloride melts and then adjust the flame so that the mixture boils gently. After 10 minutes, remove the flame and add 3 ml of water and 2 ml of 6 *N* hydrochloric acid. Cool and then filter the solid; wash twice with 2–3 ml of 10 per cent hydrochloric acid and twice with the same amount of water. Recrystallize as in Section 11.18 (page 259). The yield is 50–70 mg of crystals, melting at 86–87°.

Note: *The p-bromobenzenesulfonamides of benzylamine, ethylaniline, and piperidine* are prepared by the same procedure as described for butylamine, although the amount of alcohol required for crystallization is somewhat greater; the yield of derivatives from 100 mg of the base is about 90–110 mg.

m-Nitrobenzenesulfonyl chloride may be used to advantage in the preparation of derivatives of *diethylamine* and *di-n-butylamine*. The procedure is the same as that for the preparation of the *p*-bromobenzenesulfonamides.

In the preparation of the bromo- and nitrosubstituted sulfonamides, it is important to wash the crude derivative thoroughly with dilute hydrochloric acid since there is always a small amount of unreacted amine present.

11.21 N-Methyl-N′-phenylthiourea. Place 0.15 ml (7 drops) of phenylisothiocyanate in an 8-inch test tube; add 2 drops of methylamine solution (33 per cent) and 1 ml of methanol so that a clear solution results. Heat for 10 minutes at 60–70°; if the tube is partially immersed in the water bath, the alcohol that boils off from the mixture condenses on the sides of the tube. If the boiling is brisk, either a reflux condenser is used or an additional 1 ml of methanol is added after about 5 minutes of heating.

Add to the reaction mixture, while it is still hot, 1.5 ml of water and cool the tube in tap water; by means of a glass rod scratch the inner sides of the tube until the oil that separates at first begins to crystallize. Allow the tube to stand in the cold bath for 10 minutes; then filter. Wash first with 2 ml of water to which 1 drop of 6 *N* hydrochloric acid has been added, then with 1 ml of plain water. Transfer the solid into the 8-inch reaction tube and dissolve in about 1.5 ml of hot methanol. Filter and add to the hot solution 0.7 ml of water. Stir and scratch the inner sides of the tube until crystallization begins. Filter and wash the crystals with 1 ml of 25 per cent methanol. The yield is 110 mg of crystals, melting at 112–113°.

Note: The main disadvantage of the thioureas is that these derivatives often separate as oils from the reaction mixture and are, at times, slow in crystallizing out. The derivatives of the lower alkylamines are quite soluble in alcohol and hence water must be added for separation. The addition of water invariably causes the separation of the thiourea as an oil. Therefore, in the purification of the crude thiourea, it is advisable to save a small amount of crystals so that a minute amount may be used to seed the oily mixture that separates from the filtered solution of the derivative upon cooling.

11.22 N-di-n-Butyl-N′-phenylthiourea. Place in an 8-inch test tube 0.2 ml of phenylisothiocyanate, 0.2 ml of di-*n*-butylamine, 2 ml of

methanol, and 1.5 ml of water. Heat to simmering for about 10 minutes; then proceed as in Section 11.21 above. The yield is 180 mg of crystals, melting at 84–85°.

11.23 N-n-Amyl-N'-phenylthiourea. Place in an 8-inch test tube 0.1 ml of phenylisothiocyanate, 0.1 ml of *n*-amylamine, and 1 ml of methanol. Heat as described in Section 11.21 above for 10 minutes. Add 1 ml of water and cool for 30 minutes; the oil that separates out will change to a crystalline solid with prolonged shaking of the mixture and scratching of the inner sides of the tubes by means of a glass rod. Use 2 ml of methanol for crystallization of the thiourea and add 4–5 drops of water to the hot filtered solution. Follow the general procedure outlined in Section 11.21. The yield is 120–140 mg of crystals, melting at 69°.

Note: *o-Bromoaniline* yields a thiourea easily when the same procedure and quantities of reagents are used. The derivative is dissolved in 10 ml of methanol for crystallization and no water is added after filtration of the hot solution. The melting point of the derivative is 146°.

11.24 N-Butyl-N'-α-naphthylthiourea. Place in an 8-inch tube, provided with a condenser, 100 mg of *α-naphthylisothiocyanate*, 0.1 ml of *n*-butylamine, and 1 ml of ethanol; heat for 30 minutes in a water bath at 60–70°, or over a small free flame of the microburner, so that the alcohol boils gently. Cool and, if the solid thiourea does not separate out, add 1–2 drops of water and rub the oil that separates out against the sides of the tube by means of a glass rod until it solidifies. Add 1–2 ml of 50 per cent ethanol to facilitate the transfer of the crystals and filter by suction; wash once with 1 ml of 50 per cent ethanol and once with 1–2 ml of 90 per cent ethanol. Transfer the solid into a test tube and add 2 ml of petroleum ether; heat to boiling and then cool and filter by suction. Transfer the solid remaining on the filter to a test tube and dissolve in 3 ml of ethanol; filter by suction and add 0.5 ml of water to the hot filtrate. By means of a glass rod rub the oily emulsion against the walls of the tube until crystals begin to separate out; then cool for 15 minutes. Filter by suction and wash with 1–2 ml of 50 per cent ethanol. The melting point of the crystals is 107–108°; if a lower melting point is obtained, it indicates that the unreacted isothiocyanate and the small amount of dinaphthylthiourea were not completely removed. If the melting point is in the vicinity of 100°, repeat the process of washing with 90 per cent methanol and with petroleum ether and then recrystallize from alcohol and water. The yield of the pure thiourea varies between 75–150 mg.

Note: If an impure product is obtained, 4–5 crystallizations will be required for purification. A slight excess of amine should be used so that very little isothiocyanate remains unreacted; the proportions should be about 1.3 millimoles of the amine to 1 millimole of the isothiocyanate. Alcohols react very slowly with isocyanates and are therefore used as solvents; the alcohol may be omitted in the case of the lower amines, which react readily. The amine and isothiocyanate are heated for 1–2 minutes over a small flame of the microburner until a homogeneous solution is obtained. The mixture is then cooled while stirring with a rod; the solid mass that separates out is extracted with 90 per cent ethanol and then with petroleum ether and crystallized as directed.

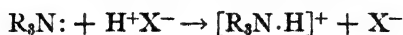
The preparation of *thioureas* is preferred to that of the corresponding *ureas* by reaction of the amine with *α-naphthyl isocyanate.* Comparative runs with the same amine indicate that far greater precautions are necessary to obtain a pure product with *α-naphthyl isocyanate* than with the corresponding *isothiocyanate.* The chief difficulty is the reaction of the isocyanate with the moisture present in the tube and in the reagent to yield dinaphthyl urea, which is difficult to separate from the alkyl or aryl-naphthylurea.

11.25 β-Naphthylamine-3,5-dinitrobenzoate. Prepare a solution of 3,5-dinitrobenzoic acid containing 212 mg of the acid dissolved in 20 ml of methanol. Weigh accurately 143 mg of β-naphthylamine and place in a small evaporating dish; add the alcoholic solution of the nitrobenzoic acid to the amine and evaporate the mixture on a water bath. Scrape the crystals and transfer into a 6-inch test tube. Add 2.5 ml of methanol, heat to boiling for a second, and then, if the solution is not complete, add more alcohol dropwise until a clear solution is obtained. Cool rapidly and allow to stand for 5 minutes. Filter and wash the crystals with 0.5 ml of methanol. The yield is 10–20 mg, melting at 195–196°. The crude, unrecrystallized derivative melts at 189–191°.

Note: This method, although effective in the identification of some aromatic amines, fails to give easily crystallizable products from such tertiary amines as dimethylaniline. Other amine salts described in the literature for the identification of amines are the 2,4-dinitrobenzoates. The original literature should be consulted; references are given on page 266.

Derivatives of Tertiary Amines

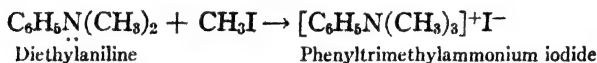
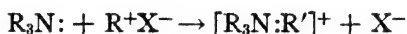
The tertiary amines do not have amino hydrogen atoms; hence the reactions by which derivatives may be made are restricted to the formation of salts. Tertiary amines act as proton-acceptors; hence they are bases and form salts with acids:

$$R_3N: + H^+X^- \rightarrow [R_3N \cdot H]^+ + X^-$$

The amine *hydrobromides* and *hydrochlorides* are not particularly suitable since they melt with decomposition at temperatures that often are dependent on the rate of heating. Chloroplatinic acid and chlorauric acid give well-defined salts with some of the tertiary amines: the use of *3,5-dinitrobenzoic* and *2,4-dinitrobenzoic* acid yields, in some instances, good results. On the other hand, many of the tertiary arylamines that are weakly basic either do not form well-defined salts, or these compounds undergo slight decomposition on crystallization due to hydrolysis or alcoholysis.

By far the most useful of the salts are the *picrates*. These are easily formed by boiling the amine with a saturated solution of picric acid in methanol. The picrates may be purified by crystallization without appreciable decomposition.

Another type of derivative is formed by tertiary amines by the acceptance of an organic radical to form quaternary ammonium salts:

$$R_3N: + R^+X^- \rightarrow [R_3N:R']^+ + X^-$$

$$\underset{\text{Diethylaniline}}{C_6H_5\ddot{N}(CH_3)_2} + CH_3I \rightarrow \underset{\text{Phenyltrimethylammonium iodide}}{[C_6H_5N(CH_3)_3]^+I^-}$$

The most useful quaternary salt types of derivatives are those formed with *methyl iodide*, *methyl-p-toluenesulfonate*, and *benzyl chloride*. The quaternary methyl-*p*-toluenesulfonates are useful in the case of nitrogen cyclic compounds and less useful with other types of amines.

A number of arylamines react with nitrous acid to give *p-nitroso* derivatives. In a few cases where other derivatives are not easily prepared, these may be used for characterization work.

11.26 Dimethylaniline picrate. Place into an 8-inch test tube 3 ml of a saturated solution of picric acid in methanol and 0.1 ml of N,N-dimethylaniline. Add 5 ml of methanol, boil for a few minutes using a reflux condenser, and allow to cool. Filter the crystals and wash twice with 1 ml of methanol. The yield is 180–200 mg of crystals, melting at 162–163°.

11.27 Quinoline picrate. Use the same procedure and the same quantities of reagents as in Section 11.26 above. The yield of quinoline picrate is 200–225 mg, melting at 202–203°.

Note: Pyridine picrate is prepared easily by the same method. The preparation of pyridine-methyl-*p*-toluenesulfonate described in the following section is given as an illustration of the general method of preparation of the methyl-*p*-toluene sulfonates.

11.28 Pyridine methyl-p-toluenesulfonate. Pour into a 6-inch test tube 0.2 ml of pyridine, 300 mg of methyl-*p*-toluenesulfonate, and 1 ml of isopropyl ether. Boil (under reflux) in a water bath for 20 minutes; then cool. Pour off the ether from the crystals and add 1 ml of methanol. Heat until a solution results and then add 5 ml of ethyl acetate. Cool and filter the product; wash with 1 ml of ethyl acetate and dry a small amount of crystals by pressing between filter paper; dry in the air for 2–3 minutes and then determine the melting point. If the melting point is below 139°, the product is recrystallized. The yield is 175–200 mg of crystals.

Note: The preparation of the methyl-*p*-toluene sulfonate is undertaken if the picrate is found unsuitable. In the case of pyridine, the picrate is easily prepared and purified.

11.29 Methyl-tri-n-butyl ammonium iodide. Place 0.1 ml of tri-*n*-butylamine and 0.1 ml of methyl iodide in a test tube and add 1 ml of isopropyl ether. Heat under reflux for 5 minutes; then cool. Filter and wash the crystals with 1 ml of isopropyl ether. The yield is 180 mg of crystals, melting at 179–180°.

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Derivatives of Amides, Imides, and Ureas

The identification of the amides, $RCONH_2$, and substituted amides $RCONHR'$, such as anilides, toluidides, and the like, is usually accomplished by hydrolysis:

$$RCONH_2 + H_2O + HCl \rightarrow RCOOH + NH_4Cl$$

$$RCONHR' + H_2O + NaOH \rightarrow RCOONa + R'NH_2$$

The hydrolytic products are characterized by methods suitable for identification of carboxylic acids and amines.

The hydrolysis of the simpler amides and substituted amides is effected by boiling the compound with 6 *N* hydrochloric acid or with a 10–20 per cent solution of sodium hydroxide. Alkaline hydrolysis is usually faster than acid hydrolysis. Amides and substituted amides that are resistant to hydrolysis when boiled with aqueous solutions of acids or bases may be hydrolyzed by heating with 100 per cent phosphoric acid. Another method for the hydrolysis of resistant amides is to heat the compound at 200° in a 20 per cent solution of potassium hydroxide in glycerol.

If acid hydrolysis is used, the reaction mixture is made alkaline in order to separate the amine. If the original compound is an amide, the ammonia is identified by its odor or it may be distilled into a receiver containing dilute hydrochloric acid and then tested with Nessler's[1] solution or chloroplatinic acid. In the case of substituted amides, the amine that separates out may be isolated either by filtration, if it is a solid, or by extraction with ether or by distillation. Two or three extractions

[1] See also Test 6.12.

with ether will remove the amine from the reaction mixture. The ether extract is shaken with a small amount of hydrochloric acid. The amine, through salt formation, passes into the aqueous layer, which is then separated, carefully neutralized, and treated with an acid chloride as described in Sections 11.14–11.20, pages 257–261.

After removal of the ammonia or amine, the remaining alkaline solution is evaporated to a small volume and carefully neutralized. This solution is used for the preparation of the *p-nitrobenzoyl ester*, as described in Section 9.7, page 212. If the acid is a solid, the concentrated alkaline solution is acidified, cooled, and the carboxylic acid that separates out is removed by filtration.

A limited number of amides (about 30) may be identified by direct derivatization without the hydrolytic step. The reactions by which the preparation of derivatives is effected are shown by the following equations:

$$2\,RCONH_2 + HgO \longrightarrow \underset{\text{Mercuric salt}}{(RCONH)_2Hg} + H_2O \qquad (1)$$

$$RCONH_2 + (COOH)_2 \longrightarrow \underset{\text{Amide oxalate}}{RCONH_2 \cdot (COOH)_2} \qquad (2)$$

$$\underset{\text{Xanthydrol}}{C_6H_4\langle{}^{CH(OH)}_{O}\rangle C_6H_4} + RCONH_2 \longrightarrow \underset{\text{N-Xanthylamide}}{C_6H_4\langle{}^{CH(NHCOR)}_{O}\rangle C_6H_4} + H_2O \qquad (3)$$

$$\underset{\text{Phthalyl chloride}}{C_6H_4\langle{}^{COCl}_{COCl}} + RCONH_2 \longrightarrow \underset{\text{N-Acylphthalimide}}{C_6H_4\langle{}^{CO}_{CO}\rangle NCOR} + 2\,HCl \qquad (4)$$

Equation (1) represents the formation of a salt through the weak acidic properties of the amides. The *mercury salts* are formed by heating a mixture of mercuric oxide and the amide in alcohol; an alternate method consists in heating a mixture of the oxide and the amide to the melting point of the latter. The melting point of 15 mercuric derivatives have been described; most of these are above 200°.

The formation of an *amide oxalate* as shown by Equation (2) is an example of salt formation through the weak, basic properties of the amides. The reaction is effected by heating anhydrous oxalic acid and the amide in presence of ethyl acetate. The derivatization of 6 lower aliphatic amides by this method has been described.

Equation (3) represents the condensation of an amide with xanthydrol

to form a *xanthylamide*. This reaction has been applied to the derivatization of about 25 amides.

Equation (4) shows the reaction of phthalyl chloride with amides to form *N-acylphthalimides*. However, no melting point data of such derivatives have been published.

The reader is also referred to the section on hydrolysis in Chapter 8.

11.30 Hydrolysis and characterization of acetanilide. Place in a small distilling tube, arranged as in Figure 62, page 178, 5 ml of 10 per cent sodium hydroxide solution and 300 mg of acetanilide. The receiving tube contains 2 ml of 10 per cent hydrochloric acid. Add 2 boiling stones into the distilling tube and boil gently for 10–15 minutes. Remove the reflux condenser from the distilling tube and place it into the receiving tube (Figure 20, page 42). Distil the reaction mixture until about 3 ml of distillate have been collected in the receiving tube containing the acid. Save the residue in the distilling tube for identification of the acid.

Add to the tube containing the distillate 5 ml of 10 per cent sodium hydroxide and 0.2 ml of benzenesulfonyl chloride and proceed according to the directions given in Section 11.15, page 258.

Pour the alkaline residue remaining in the distilling tube into an 8-inch tube. Wash the distilling vessel with 1–2 ml of water and add the washings to the mixture in the 8-inch tube. Add a drop of phenolphthalein and then cautiously dilute hydrochloric acid as described under the hydrolysis of isopropyl acetate, page 232, section 10.12, second paragraph.

Note: Certain acyl-substituted amides, particularly those containing nitro and halogen groups, are resistant to hydrolysis. In such cases use is made of 100 per cent phosphoric acid. About 300–400 mg of the amide are placed in a tube containing a mixture of 1.0 g 85 per cent phosphoric acid and 400 mg of phosphorous pentoxide. The mixture is boiled gently with a very small flame for 1 hour under reflux to effect hydrolysis. The hydrolytic products are treated in the manner outlined.

11.31 Xanthyl derivative of acetamide. Place 500 mg of xanthydrol and 4 ml of glacial acetic acid in an 8-inch tube. Shake at intervals for 5 minutes until the xanthydrol dissolves. If an oil separates, decant the supernatant solution into another tube. Add to the xanthydrol solution 250 mg of acetamide, cork, and set aside for 2 hours. Filter off the solid and recrystallize it from a mixture of 70 per cent dioxane and 30 per cent water. The yield is 100–120 mg of crystals, melting at 238-240° uncorrected.

Note: If the xanthyl derivative does not separate within 2 hours, the mixture is allowed to stand overnight or is heated at 80–90° for 30 minutes and then cooled.

11.32 Mercuric derivative of benzamide. Place in an 8-inch tube arranged for reflux 300 mg of benzamide, 400 mg of finely powdered mercuric oxide, and 4 ml of methanol. Add a boiling stone and boil gently for 30 minutes. Filter the hot mixture with suction. Cool the filtrate in an ice-water mixture for 10–15 minutes. Filter off the solid and wash with 1–2 ml of cold methanol. The yield is 90–100 mg of crystals, melting at 222° uncorrected.

Note: An alternate method for the preparation of the mercury derivatives is to place the mixture of amide and mercuric oxide in an 8-inch tube and then heat by means of a small flame until the amide melts and the reaction begins. If the yellow color is not discharged, more amide is added in small portions until the color is removed completely. The mixture is heated for a few minutes and then allowed to cool. About 3–4 ml of alcohol are added and the mixture is heated until the solid dissolves; the solution is allowed to crystallize.

Since the derivatives of aliphatic amides are soluble in cold ethanol and methanol, the amount of solvent should be regulated. On the other hand, the derivatives of aromatic amides have low solubilities and in certain cases purification is effected by leaching out the unreacted amide with boiling alcohol

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Derivatives of Amino Acids

The amino acids listed in Table 23 are for the most part *α-aminocarboxylic acids* derived from proteins by hydrolysis. The three isomeric aminobenzoic acids are included in the same table. They are characterized by similar derivatives, although they do not bear close relation either to the physical properties of the α-aminocarboxylic acids or to their chemical reactions.

The α-aminocarboxylic acids are nonvolatile compounds, which for the most part melt above 200° with extensive decomposition; this property is assumed to be due to the dipolar structure of the solid state. Since the melting of the crystalline solid is accompanied by decomposition, there is no fixed temperature at which the solid and liquid phase coexist, but *a temperature range at which decomposition takes place;* further, this decomposition range depends on the *rate of heating.*[1] As a consequence there exists a considerable confusion in the literature as to the so-called "melting points" of amino acids. A few examples will serve as illustrations: *d*-glutamic acid has been reported to melt with decomposition at various temperatures from 198° to 225°. *l*-Tyrosine decomposes according to Fischer with rapid heating at 314–8° (corr.) and with slow heating at 290–5°; the same compound has been reported to decompose at 344°. Similarly *dl*-Tyrosine has been reported to decompose at 295°, 318°, and 340°. The nature of the difficulty is shown by the decomposition point of thyroxine; if heated at 10° per minute, it melts at 250°, and if heated at 3° per minute, it melts at 230–5°. In most cases if the compound is quickly heated it decomposes at a higher temperature than when heated slowly; the difference may be as high as 40–50°. This brief discussion shows that since the decomposition points are very unreliable, they cannot be used except to indicate a range of possibilities. Therefore it is advisable, in the determination of the melting point of a substance suspected to be an α-aminocarboxylic acid, to make determinations both with rapid and slow heating of the bath.

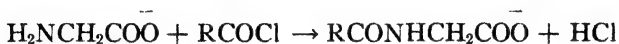
The reactions used to prepare solid derivatives of the amino acids are those that characterize the amino group. For the purpose of discussion these reactions are divided into three groups.

1. *Acylation.* The following derivatives have been found useful: *acetyl, formyl, benzoyl, 3,5-dinitrobenzoyl, benzenesulfonyl, p-toluenesulfonyl, β-naphthalenesulfonyl,* and *4-nitrotoluene-2-sulfonyl.* The usual procedure is to shake an alkaline solution of the amino acid with an

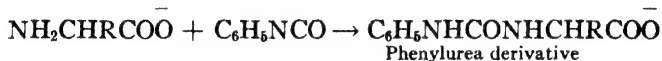
[1] See the discussion on page 39

equivalent amount of the acid chloride. The reaction in most cases takes place very slowly, often requiring 3–4 hours of mechanical shaking. This slowness is probably due to the inability of the amino group to react in the charged (dipolar) form; the addition of alkali increases the concentration of the form having a free amino group:

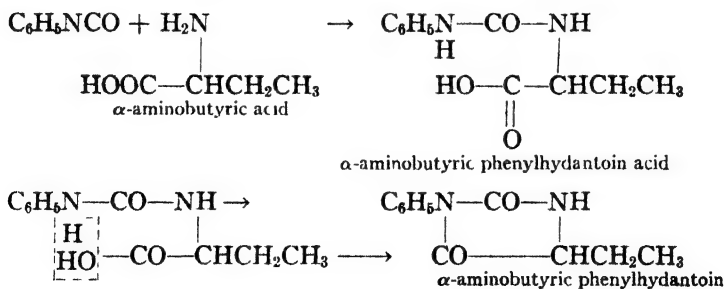
$$\overset{+}{N}H_3CH_2CO\overset{-}{O} + NaOH \rightarrow NH_2CH_2CO\overset{-}{O} + \overset{+}{Na} + HOH$$

$$H_2NCH_2CO\overset{-}{O} + RCOCl \rightarrow RCONHCH_2CO\overset{-}{O} + HCl$$

For the beginner the use of 3,5-dinitrobenzoyl chloride is recommended wherever possible, since the reaction requires only a few minutes of shaking.

2. *Formation of substituted ureas.* Amino acids react with isocyanates in an analogous manner as amines, to form N-substituted ureas:

$$NH_2CHRCO\overset{-}{O} + C_6H_5NCO \rightarrow \underset{\text{Phenylurea derivative}}{C_6H_5NHCONHCHRCO\overset{-}{O}}$$

The phenyl or α-naphthylureido derivatives are prepared by shaking a solution of the amino acid in sodium or potassium hydroxide with phenyl or α-naphthylisocyanate until the odor of the latter disappears; the derivatives called hydantoin acids separate mostly as gelatinous precipitates, which may be converted to a crystalline form through careful crystallization from water-alcoholic mixtures. The hydantoin acid, when boiled with 10 per cent hydrochloric acid solution for a short time (3–5 minutes), undergoes ring closure by elimination of water to form the *hydantoin* as shown by the following equations:

$$C_6H_5NCO + \underset{\alpha\text{-aminobutyric acid}}{H_2N{-}CH(CH_2CH_3){-}COOH} \rightarrow \underset{\alpha\text{-aminobutyric phenylhydantoin acid}}{C_6H_5NH{-}CO{-}NH{-}CH(CH_2CH_3){-}C(=O){-}OH}$$

$$C_6H_5N(H){-}CO{-}NH{-}CH(CH_2CH_3){-}CO{-}OH \longrightarrow \underset{\alpha\text{-aminobutyric phenylhydantoin}}{C_6H_5N{-}CO{-}NH{-}CHCH_2CH_3{-}CO \text{ (ring)}}$$

The hydantoins are easily crystallized from alcohol solutions and, when their formation is possible, they are preferable to the corresponding hydantoin acid. Reference to Table 23 shows that the majority of the substituted ureas and hydantoins are phenyl derivatives. This fact is due to the earlier use of phenyl isocyanate as a reagent for the amino group; since there is less danger of toxicity in the use of α-naphthyl-

isocyanate, it is believed that the α-naphthylurea derivatives and the corresponding hydantoins are more suitable for characterization work.

3. *Reaction with polynitro compounds. Picric acid, flavianic acid (naphthol yellow S, or the sodium salt of 1-naphthol-2,4-dinitro-7-sulfonic acid), and picrolonic acid (nitrophenyl-nitromethylpyrazolone)* form salts with many amino acids, which may be used for characterization. The picrolonates are stated to have sharper melting points than the picrates.

With reference to the melting points of the derivatives of the amino acids, there exists somewhat the same condition (but to a less degree) as with the decomposition points of the individual amino acids. The melting point of the benzoyl derivatives of *d* or *l*-glutamic acid is given as 138°, 130–132°, and 137–139°; the figure 130–132° seems to be the most probable value. Similarly, the melting point of glycine phenylurea has been given as 197°, 195°, 208°, and 163°, the first figure representing the most likely correct value. Therefore it is recommended that the beginner should prepare a derivative from a known sample of the amino acid identified as the unknown and proceed to determine the melting point, using the same procedure as for the derivative of the unknown sample.

11.33 Preparation of 3,5-dinitrobenzoates of amino acids. Dissolve 200 mg of the amino acid in 5–6 ml of 1 *N* sodium hydroxide (dilute 1 ml of 6 *N* solution to 6 ml) in an 8-inch tube. Add the calculated amount of finely powdered 3,5-dinitrobenzoyl chloride; stopper tube with a No. 5 solid rubber stopper, shake vigorously for 2 minutes, and allow to stand for 5 minutes, shaking if particles of the chloride remain undissolved. Add dilute hydrochloric acid to *p*H 4–5 (use Congo red or Universal indicator). Filter the crystals and wash with 2 ml of dilute (25 per cent) alcohol.

Note: The monoamino dicarboxylic acids react less vigorously than the monocarboxylic acids, and in this manner separation between the monoamino and diamino may be effected. Tyrosine does not react with the acid chloride; the diamino acids react usually with two moles of the chloride, forming bis(3,5-dinitrobenzoyl) derivatives.

11.34 Preparation of p-toluenesulfonyl derivatives of amino acids. Place 300 mg of the amino acid in a small glass-stoppered bottle; the stopper should be well ground and flat at the top so that it may be wired across in order to prevent its becoming loose during shaking. Place in the bottle 3 millimoles of the amino acid and 7 ml of 1 *N* sodium hydroxide solution. Add 700 mg of *p*-toluenesulfonyl chloride dissolved in 5 ml of ether. Place a minute amount of vaseline on the upper part of the

stopper and fit it into the bottle, turning slightly so as to make a tight fit. Wire the stopper and shake the bottle at frequent intervals over a period of several hours. If a shaking machine is available, shake mechanically for 3 hours. Separate the ethereal layer and acidify the aqueous solution to *p*H 4–5 (use Congo red or Universal indicator). Cool the solution for an hour; if the derivative separates as an oil, induce crystallization by scratching the inner walls of the vessel. Crystallize twice by dissolving the derivative in hot alcohol, filtering the hot solution and adding water cautiously until a permanent cloudiness results.

Note: The original article by McChesney and Swann (see Bibliography) should be consulted for the preparation of the derivatives of the dicarboxylic acids, of tyrosine, and alanine. The following amino acids yield oils that do not crystallize: glutamic, aspartic, arginine, lysine, tryptophane, and proline.

11.35 Preparation of α-naphthylurea derivatives of amino acids. Use an 8-inch tube provided with a solid rubber stopper. Place 3 millimoles of the amino acid dissolved in 3 ml of 1 *N* sodium hydroxide solution and 5 ml water. Add 0.6 ml of α-naphthylisocyanate, stopper the tube, and shake for 2–3 minutes; then allow to stand for 30–45 minutes with occasional shaking. Filter the insoluble α-naphthylurea and acidify the filtrate to *p*H 4–5 (use Congo red or Universal indicator). The α-naphthylhydantoin acid separates out on cooling for an hour. Dissolve the derivative in hot alcohol, filter, and add cautiously a few drops of water until a permanent cloudiness results; then cool.

Note: For cystine it is advisable to use very dilute potassium hydroxide (250 mg cystine 2 ml 1 *N* sodium hydroxide, and 20 ml water), since the sodium salt is difficultly soluble.

11.36 Preparation of phenylhydantoins of amino acids. Dissolve 200 mg of the amino acid in 2 ml of 1 *N* potassium hydroxide solution and 3 ml of water. Add 200 mg of phenylisocyanate. (**Caution:** *Use care since phenylisocyanate is toxic.*) Stopper the tube with a solid rubber stopper and shake until the odor of isocyanate disappears. Filter with suction and neutralize with dilute hydrochloric acid solution to *p*H 4–5 (use Congo red or Universal indicator). A gelatinous precipitate separates out on cooling. Filter the precipitate and transfer it by means of a microspatula into an 8-inch tube. Add 5 ml of 10 per cent hydrochloric acid solution in such a manner as to wash the hydantoin acid down into the tube. Boil gently for about 3 minutes and then cool when needles of the hydantoin separate out. Crystallize from alcohol; the yield is 200–250 mg.

Selected References on Amino Acids

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Preparation of Derivatives—Continued

Derivatives of Halogen Compounds

THE reactions of alkyl and cycloalkyl halides that can be used for their identification are illustrated by the following equations:

$$\underset{}{C_2H_5Br} + 2\,\underset{\text{Thiourea}}{NH_2CSNH_2} \longrightarrow \underset{\text{S Ethylisothiourea}}{NH_2CS(NH)C_2H_5} + NH_2CSNH_3{}^+Br^- \quad (1)$$

$$NH_2S(NH)C_2H_5 + \underset{\text{Picric acid}}{C_6H_2(OH)(NO_2)_3} \longrightarrow \underset{\text{S-Ethylisothiourea picrate}}{NH_2S(NH)C_2H_5 \cdot C_6H_2(OH)(NO_2)_3}$$

$$CH_3I \xrightarrow[(C_2H_5)_2O]{Mg} CH_3MgI \quad (2)$$

- $+ \underset{\alpha\text{-Naphthyl-isocyanate}}{C_{10}H_7NCO} \longrightarrow \underset{\text{Aceto-}\alpha\text{-naphthalide (N-}\alpha\text{-naphthylacetamide)}}{CH_3CONHC_{10}H_7}$
- $+ \underset{\text{Phenyliso cyanate}}{C_6H_5NCO} \longrightarrow \underset{\text{Acetanilide}}{CH_3CONHC_6H_5}$
- $+ \underset{p\text{-Tolylisocyanate}}{C_6H_4(CH_3)NCO} \longrightarrow \underset{\text{Aceto-}p\text{-toluidide}}{CH_3CONHC_6H_4CH_3}$

$$CH_3I \xrightarrow[(C_2H_5)_2O]{Mg} CH_3MgI + HgI_2 \longrightarrow \underset{\text{Methyl mercuric iodide}}{CH_3HgI} + MgI_2 \quad (3)$$

$\underset{n\text{-Butyl Bromide}}{C_4H_9Br}$ (4)

- $+ \underset{\text{Potassium phthalimide}}{C_6H_4(CO)_2N \cdot K} \longrightarrow \underset{\text{N-}n\text{-butyl phthalimide}}{C_6H_4(CO)_2N \cdot C_4H_9} + KBr$
- $+ \underset{\text{Sodium saccharin}}{C_6H_4(CO)(SO_2)N \cdot Na} \longrightarrow \underset{\text{N }n\text{-butyl saccharin}}{C_6H_4(CO)(SO_2)N \cdot C_4H_9} + NaBr$

C_2H_5I (5)

- $+$ Triiodophenol (OH; I, I, I) $\xrightarrow{NaOC_2H_5}$ Triiodophenyl ethyl ether (OC_2H_5; I, I, I) $+ NaI + C_2H_5OH$
- $+$ *p*-Hydroxybenzoic acid (COOH, OH) $\longrightarrow$ *p*-Carboxyphenyl ethyl ether (COOH, OC_2H_5) $+ HI$

$$CH_3CH_2CH_2I + \text{Silver-3,5-dinitrobenzoate } (C_6H_3(NO_2)_2COOAg) \longrightarrow n\text{-Propyl-3,5-dinitrobenzoate } (C_6H_3(NO_2)_2COOCH_2CH_2CH_3) + AgI \quad (6)$$

$$CH_3CH_2Br + \beta\text{-Naphthol } (C_{10}H_7OH) \xrightarrow{NaOH} \text{Ethyl } \beta\text{-naphthyl ether } (C_{10}H_7OC_2H_5) + NaBr + H_2O \quad (7)$$

Equation (1) represents the formation of *S-alkylisothiourea picrates.* These molecular compounds, whenever they can be prepared, should be among the first derivatives to be tried. They are easily obtained in good yields by heating a mixture of the halide and thiourea. The mixture, dissolved in ethanol, is refluxed for 15 to 30 minutes; then a saturated alcoholic solution of picric acid is added and the vessel cooled. The picrate of the S-alkylisothiourea separates out. The addition compound is recrystallized after filtration. If the organic halide is a chloride, a small amount of potassium iodide is added to the reaction mixture; the addition of potassium iodide increases the reactivity of the chloride, but it is not very effective with a number of chlorides. Therefore, the mixture of thiourea and halide should be heated for 2 or 3 hours. For example, *n*-butyl chloride and thiourea must be refluxed for 2 hours and *n*-propyl chloride for 5 hours, in order to obtain satisfactory results. The number of halides from which S-isothiourea picrates have been obtained is about 25; however, among these are the most common alkyl halides—that is, those that have 1 to 5 carbon atoms.

The reactions represented by Equations (2) and (3) are based on the conversion of the halides to a Grignard reagent, which may be reacted either with an *isocyanate* to form a *substituted amide* or with a *mercuric halide* to form an *alkylmercuric halide.* The preparation of the Grignard reagent requires some care (see pages 187–193). If the reagents are pure, the semimicro preparation should be complete within one-half hour. Once prepared, the Grignard reagent should be reacted immediately, either with the isocyanate or with the inorganic mercuric halide.

The selection of the isocyanate depends upon the availability of the reagent and the probable nature of the halide. For the lower halides α-naphthylisocyanate is preferable, due to the lower solubilities of the *naphthalides* as compared with the corresponding *anilides.* For the higher halides either phenylisocyanate or *p*-tolylisocyanate may be used.

The side reactions of the isocyanates have been discussed in connection with the identification of alcohols (page 219). The formation of ureas

through the reaction of isocyanates with moisture present in the vessel and reagents necessitates extraction of the substituted amide with petroleum ether. In general, two crystallizations are necessary for purification of the product obtained by extraction of the crude mixture with petroleum ether; however, in some cases 3 or 4 crystallizations may be necessary. The use of alcohol as a recrystallization solvent, although it is given in the literature, is not recommended for semimicro work. The solubility of the substituted ureas formed by side reactions is greater in methanol or ethanol than in petroleum ether; hence their elimination by crystallization, when alcohol is used as a medium, is more difficult. When 90 per cent methanol is used to recrystallize the crude naphthalide obtained from the reaction of methyl magnesium iodide and α-naphthylisocyanate, it usually requires about 4 or 5 crystallizations to obtain a pure product, whereas when petroleum ether is employed, 1 or 2 crystallizations are sufficient.

The Grignard reagent from the alkyl halide may be converted to an alkyl mercuric halide by addition of the corresponding mercuric halide; if, for example, an organic bromide was employed to prepare the Grignard reagent, mercuric bromide is used. Although in some cases it is possible to obtain good yields with as little as 0.1 ml of the halide, it is advisable in semimicro work to use 0.3–0.5 ml of the halide for the preparation of the alkyl mercuric halides. The crystallization of some of the organomercuric compounds is slow and purification difficult at times. Other precautions are discussed in the experimental section dealing with the preparation of alkylmercuric halides.

Equation (4) represents the use of *aromatic cyclic imides* for the preparation of derivatives from halides. Potassium phthalimide, potassium 3-nitrophthalimide, and sodium saccharin (sodium *o*-sulfobenzimide) yield well-defined crystalline derivatives when boiled with alkyl halides. The time required for the reaction is usually 1 to 2 hours; the yields of the pure derivatives when semimicro quantities are employed are not of sufficient magnitude to warrant their preparation before other derivatives are tried. Since sodium saccharin is commercially available and at a low price, its use for beginners is preferable if this type of derivative is considered.

Equations (5) represent the use of *substituted phenolic ethers* for the preparation of derivatives from alkyl halides. When triidophenol or *p*-hydroxybenzoic acid are refluxed with an alkyl halide in the presence of a condensing agent, the hydroxyl group reacts with the halogen to form an ether.

Equation (6) shows the formation of an ester by reaction of the *silver*

salt of 3,5-dinitrobenzoic acid and the alkyl iodide. The method is applicable to a number of alkyl iodides but does not give satisfactory results with the corresponding chlorides or bromides. The alkyl iodide, dissolved in a small amount of alcohol, is heated with a slight excess of dry, finely powdered silver dinitrobenzoate. The reaction mixture is evaporated to dryness and extracted with ether to remove the ester. The crude ester is then purified (page 221). For the application of this method to organic chlorides, the reader is referred to the literature (see page 287).

Equation (7) represents the formation of an *alkyl β-naphthyl ether*. This reaction has been discussed in connection with the derivatization of ethers (page 236), and also under alkylation, page 183.

Aryl halides. The relatively slow rates of reaction of halogen atoms when they are attached to benzene nuclear carbon atoms render most of the reactions discussed in the preceding section inapplicable. Whenever it is feasible to prepare Grignard reagents from the aromatic halides, the *anilide*, *p-toluidide*, or *naphthalide* may be prepared. Generally, however, reactions that aromatic halides undergo with ease, such as nitration, are of greater use for derivatization than those described for the alkyl halides. The preparation of a *nitro derivative* of an aromatic halide should be the first reaction tried.

For the preparation of mononitroderivatives the halide is dissolved or dispersed in concentrated sulfuric acid and then treated with an equal volume of concentrated nitric acid. The mixture is frequently shaken and kept at 45–55° for 5 minutes and then diluted with water.

An alternate method that is particularly applicable to the mononitration of micro quantities is to treat the nitro compound with specially prepared 100 per cent nitric acid. About 50 mg of the compound are mixed with 75–300 mg of the acid and kept at room temperature, or heated at 45–50°, for 5–15 minutes. The mixture is then diluted with water, and the product separated and crystallized. When two or three nitro groups are to be introduced, one of the following mixtures is used: (a) fuming nitric acid and concentrated sulfuric acid; (b) specially prepared 100 per cent nitric acid and concentrated sulfuric acid; (c) fuming sulfuric acid and nitric acid described under (a) or (b).

The selection of the proper procedure is of importance in obtaining nitro derivatives. For example, consider the nitration of chlorobenzene. A search in the literature discloses the following nitro derivatives: 2-nitro, M.P. 32°; 4-nitro, M.P. 83°; 3-nitro, M.P. 44°; and 2,4-dinitro, M.P. 52°. The desirable derivatives are 4-nitrochlorobenzene and 2,4-dinitrochlorobenzene. Since there are no precise directions in the literature for obtaining these derivatives starting with about 100 mg of chlorobenzene,

the experimental condition and procedures can be easily determined by a series of test-tube experiments. In the following trials 50 mg of chlorobenzene were treated with the quantity (mg) of acid appearing outside the parentheses, while the numbers within the parentheses represent the melting-point of the crude product before crystallization: (a) 150 conc. $-HNO_3$ and 200 conc. $-H_2SO_4$ for 15 minutes at 50° (61–4); (b) 150 fuming HNO_3 for 15 minutes at 25° (oil); (c) 300 $HNO_3-100\%$ for 5 minutes at 25° (81–82); (d) 150 fuming HNO_3 and 300 conc. $-H_2SO_4$ for 15 minutes at 50–55° (30–34); (e) same as in (d), but heated at 60° for 30 minutes (40–44); (f) 150 fuming HNO_3 and 300 fuming H_2SO_4 for 30 minutes at 80–90° (48–50). From these results it is possible to select procedure (c) to obtain the mononitro derivative melting at 83° and procedure (e) or (f) to obtain the dinitro derivative melting at 52°. It is also clear from these results that several crystallizations would be required to remove the undesirable nitro derivatives from the crude nitration product. In most cases of nitration the formation of more than one nitro compound is the rule rather than the exception; therefore several crystallizations are necessary for purification of nitro derivatives.

Other reactions for the preparation of derivatives of aromatic compounds depend on the nature of the substituents present. The following is a brief enumeration; in all cases, however, other reactions should be considered if the results from nitration are unsatisfactory.

1. Reactive bromo and iodo aromatic compounds may be converted into Grignard reagents and these reacted with isocyanates. Bromobenzene, for example, may be derivatized by converting it to phenylmagnesium bromide and then to the naphthalide.

2. Side chains, particularly methyl groups, are oxidized to the carboxylic stage. Thus the chloro, bromo, and iodo toluenes with one C may be readily oxidized to the corresponding halobenzoic acids.

3. Naphthalene and some other polycyclic compounds, as, for example, the α-chloro and β-chloronaphthalenes, may be derivatized by preparation of the picrates.

4. A number of aryl halides react with chlorosulfonic acid to yield arylsulfonyl chlorides, which may be readily converted to the sulfonamides (see page 324). This reaction may be complicated by nuclear chlorination and, in a few cases, by the formation of sulfones.

The brief discussion above indicates that whenever nitration is not feasible, a judicious selection of the reaction to be employed for derivatization depends on the probable nature of the aromatic halide. A search of the literature will, in most cases, suggest the proper derivative to be

prepared. For example, in the derivatization of 3,4-dichloro-1-nitrobenzene, one of the halogens may be ammonolyzed to form a chloronitroaniline (m.p. 104–105°). The ammonolysis requires heating of the aromatic halide with alcoholic ammonia at 210°—that is, under pressure. An easier method for derivatization of this compound, which contains activated halogen due to the presence of the nitro group, is to react it with morpholine.[1] The halogen compound is refluxed for 2–3 hours with 2–3 moles of morpholine; the reaction mixture is treated with an excess of dilute hydrochloric acid, and the insoluble product is separated and crystallized from aqueous alcohol. The morpholine derivative of 3,4-dichloro-1-nitrobenzene melts at 127°. Other aromatic halides that give derivatives with morpholine are *o*-nitrochlorobenzene, *p*-nitrochlorobenzene, 2,4-dinitrochlorobenzene, and 3,5-dinitro-2-chlorobenzoic acid.

Polyhalides. The preceding paragraph applies to most aromatic polyhalides; thus the derivative to be prepared depends on the probable nature of the compound.

The characterization of the nonaromatic polyhalides is based primarily on their physical constants. In some instances, however, derivatization is possible.

12.1 S-Ethylisothiourea picrate. Place 300 mg of thiourea in a test tube and add 5 ml of ethanol or methanol and 0.2–0.25 ml of ethyl bromide. Attach to the tube a microcondenser and reflux the mixture for 15–20 minutes. Remove the flame and add 1 ml of a saturated alcoholic solution of picric acid. Boil the mixture for a short time (3–5 minutes), or until a clear solution results, and then cool in an ice-water mixture or in running cold water for 10 minutes. Filter the crystals and wash twice with 1 ml of 50 per cent alcohol. Save a very small amount (5 mg) of the derivative and crystallize the remainder. Use 2 ml of hot alcohol to effect solution of the picrate and add 1 ml of water to the filtered solution. Cool for 10 minutes and filter the crystals, washing twice with 1 ml of 50 per cent methanol. Dry the crystals in air or in a desiccator. The yield is 40–50 mg of crystals, melting at 187–188°.

Note: The same general method is used for the preparation of the alkyl isothiourea picrates from alkyl bromides and iodides. For chlorides the method is the same, except that potassium iodide is added to the reaction mixture to increase the reactivity of the halogen; this is illustrated in the preparation of the picrate from benzyl chloride described in Section 12.2.

The crystallization of the alkylisothiourea picrates may be accomplished

[1] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **70**, 406 (1937).

from hot solutions. When the conversion of the halide to the alkylisothiourea is incomplete, the melting point of the picrate after one crystallization is 6–10° lower than the value of the pure compound. In such cases it is often more time-saving to repeat the preparation of the derivative and increase the time of refluxing the halide-thiourea mixture to 30–40 minutes; in some cases (isopropyl bromide) 2–3 hours heating is necessary.

The yield of the picrate from 0.2–0.25 ml of alkyl bromides or iodides varies from 40 to 200 mg. Generally the higher primary alkyl halides give better yields than the lower halides or the secondary halides. For example, from 200 mg of the halide the following yields of the pure picrate were obtained: methyl iodide, 50 mg; *n*-propyl iodide, 60 mg; *n*-amyl bromide, 150 mg; and *sec*-amyl bromide, 50 mg.

12.2 S-Benzylthiourea picrate. The same procedure is employed as in the preceding preparation. Use 0.2 ml of benzyl chloride, 200 mg of thiourea, 200 mg of potassium iodide, and 5 ml of ethanol. Reflux for 30 minutes; then add 1 ml of the saturated picric acid solution and heat for 10 minutes. Cool, filter, and purify as described in 12.1. The yield of the pure product is 60–70 mg, melting at 188°.

Note: Chlorides, such as *n*-butyl, *n*-amyl, and the like, require longer periods of time for the formation of the alkylisothiourea. The potassium iodide is first dissolved in 2–3 drops of water, heating slightly to effect solution, and then the alcohol, thiourea, and the chloride are added in the order named.

12.3 Conversion of n-butyl bromide to n-valero-α-naphthalide (*N-α-naphthylvaleramide*). Prepare the Grignard reagent according to directions on page 191. Use 300 mg of *n*-butyl bromide, 5 ml of anhydrous ether, and 100 mg of clean magnesium turnings. After the initial reaction has subsided, heat by means of a very small flame of the microburner or by a water bath for 20–30 minutes. Then immerse the tube in cold water. Mix 5 ml of anhydrous ether and 0.2 ml of α-naphthylisocyanate in a dry test tube; add this mixture in small portions to the Grignard reagent and allow to stand for 15 minutes. Decompose the intermediate by slowly pouring the reaction mixture into a tube—containing 5 ml of water and 5 ml of dilute hydrochloric acid—so that any unreacted magnesium adheres to the sides of the reaction tube. Use 2 ml of ordinary ether to wash the reaction tube and add the washings to the mixture being hydrolyzed. Stir the mixture cautiously to insure complete hydrolysis. Transfer to a separatory funnel and draw off the aqueous layer. If a solid separates out and remains suspended in the aqueous layer, filter it off and add it to the ether solution. Transfer the ether layer to a small evaporating dish and evaporate to dryness on a steam bath. Pulverize the residue by means of the microspatula and

transfer into a 6- or 8-inch tube. Extract successively with two 5-ml portions of hot petroleum ether. Filter off the solution by suction from the undissolved impurities after first preparing the filter funnel according to directions given under the preparation of urethans (page 224) Cool the petroleum ether extracts. Filter the crystals and save the filtrates, since a further quantity of the derivative may be obtained by their evaporation. Crystallize the solid from 6–7 ml of hot petroleum ether. The yield of pure crystals, melting at 111–112°, is 45–55 mg.

Note: The amount of halide employed for the preparation of the Grignard reagent may be reduced to 0.1 ml, but precautions to prevent losses should be taken; for example, it is possible to start with 0.1 ml of methyl iodide and obtain 40–50 mg of the pure aceto-α-naphthalide if the circulation of cold water in the microcondenser (during the preparation of methylmagnesium iodide) is rapid. Since the success of the preparation depends on the completeness of conversion of the halide to the Grignard reagent, proper precautions should be taken to insure that the vessel and the reagents are dry and that the magnesium turnings are clean.

The amount of isocyanate used is in excess of that required, and therefore some substituted naphthylurea is admixed with the naphthalide; petroleum ether does not dissolve the urea; hence it is a better crystallizing medium than methanol or ethanol.

12.4 Conversion of n-amyl chloride to n-capranilide (*N-phenylcapramide*). The procedure is the same as that described in the preceding preparation except that 0.2 ml of phenylisocyanate is used in place of the α-naphthylisocyanate. Addition of a few iodine crystals to activate the magnesium metal is employed both at the beginning of the preparation of the Grignard reagent and also after the mixture has refluxed for 20 minutes, and the heating of the ether-halide-magnesium mixture is increased from 30 to 45 minutes. (**Caution:** *Care should be exercised in the handling of phenylisocyanate, owing to its lachramatory properties.*) The yield of the pure anilide is 35–40 mg.

12.5 n-Butyl mercuric bromide. Prepare the Grignard reagent in an 8-inch tube from 100 mg of magnesium turnings, 5 ml of dry ether, and 0.3 ml of *n*-butyl bromide (see page 191). The mixture is refluxed for 30 minutes. Filter the Grignard reagent into an 8-inch tube containing 1.5 g of mercuric bromide. Use a small funnel with a glass wool plug for the filtration. Stopper the tube and shake the mixture vigorously; warm the tube cautiously by momentary immersion in the steam bath and then repeat the vigorous shaking. Place the tube in a water bath and evaporate to dryness. Add 7 ml of ethanol and heat the tube in a water bath until the alcohol boils; then filter; add 3.5 ml of water to the

solution and place in an ice bath. After 30 minutes filter off the crystals, wash, and crystallize from 7–8 ml of 60 per cent ethanol. The yield of the pure compound, melting at 134–135°, is 200–220 mg.

Note: The above procedure may be used for the preparation of a number of alkyl mercuric bromides and iodides and a few alkyl chlorides. The mercuric halide used to react with the Grignard should have the same kind of halogen atom as the organic halide; thus, when an organic chloride is used, mercuric chloride is added to the Grignard reagent; otherwise mixtures of the organomercuric halides will result.

The number of crystallizations required varies with the compounds. Generally, the lower alkyl halides, having 1–3 carbon atoms, require a greater number of crystallizations to obtain pure derivative than the higher halides. For example, in comparative runs of ethyl bromide and *n*-butyl bromide, the former required 3 crystallizations to raise the melting point from 185° to 192°, whereas in the case of *n*-butyl bromide, only one crystallization was necessary. This fact would indicate that the lower halides, being more reactive, undergo side reactions.

12.6 General methods for nitration. For the introduction of one nitro group in compounds that undergo nitration with ease, proceed as follows: place 200 mg of the compound to be nitrated in an 8-inch test tube; add first 2 ml of concentrated sulfuric acid; immerse the tube in a beaker containing cold water and add slowly 2 ml of concentrated nitric acid, shaking the tube from time to time so as to prevent a rise in temperature. Place the tube in a water bath at 50–55° and heat for 15–20 minutes. The tube is shaken frequently to insure better contact of the halide with the nitrating mixture. After heating, the tube is cooled for a minute or two, and then its contents are poured into another tube, which contains 8–10 ml of cold water. The diluted mixture is returned into the original tube and cooled. The nitro compound that separates is filtered and washed twice with 3–4 ml of water; it is then transferred to the reaction tube and dissolved in the minimum amount of boiling methanol or ethanol. The hot solution is filtered, and water is added cautiously dropwise until a permanent cloudiness appears. The tube is heated until the solution is clear, and then it is cooled. The crystallization is repeated until the crystals from two successive crystallizations give a variation of 0.5–1° in the melting point.

For the introduction of two nitro groups or one nitro group in unreactive halides, the same procedure is used as described in the preceding paragraph, but fuming nitric acid is used in place of concentrated nitric acid. (**Caution:** *Care should be exercised in handling fuming nitric acid; its addition to the mixture of sulfuric acid and halide should be at such rate*

that no great amount of brown fumes appear.) The mixture is then heated at 45–50°. If the melting point of the nitration product after one crystallization shows a difference of 10° or more from the value listed in the literature, the nitration is repeated and the temperature is raised first to 80°; if the result is not satisfactory, the nitration is repeated at 90–100°.

The alternative procedure for mononitration briefly discussed on page 279 may be used, especially when the compound to be nitrated is less than 100 mg. The first step is to prepare 100 per cent nitric acid, since the fuming nitric acid available commercially is seldom above 88 per cent nitric acid. To prepare 100 per cent nitric acid, arrange a tube of 8–10 mm tubing as directed for Figure 58*A*, page 88. Place in the bulb of the tube (by means of a pipette dropper), 0.7 ml of concentrated nitric acid and 1 ml of concentrated sulfuric acid. Cool the bulb of the tube and draw out as directed for Figure 58*C*, being very cautious in the operation. Place the small delivery tube of the constructed microretort inside a 3-inch test tube. Mark by means of a label the height from the bottom of the tube that would correspond to 0.3 ml. Place the 3-inch test tube in a 50 or 100 ml beaker containing water and arrange the delivery tube of the microretort so that it is just above the 0.3 ml mark. Heat cautiously by means of a microburner until about 0.3 ml of distillate has been collected in the 3-inch tube. Discontinue heating and then remove the 3-inch tube and stopper it. The distillate is light yellow and contains 99.5–100 per cent nitric acid; if 0.5 ml of distillate is collected, the strength of the acid drops below 95 per cent.

For mononitration 50 mg of the compound are placed in a 3- or 4-inch tube and 0.1 to 0.2 ml of the prepared nitric acid is added. If the compound is very reactive, the amount used is 0.1 ml and the tube is allowed to stand at room temperature for 15 minutes; about 2 ml of water is added and the tube is chilled. The crystals are filtered and crystallized from alcohol. If the melting point differs more than 10° from that of the desired derivative, a second trial is made, using 50 mg of the compound, and 0.2 ml of the nitric acid, and heating the tube for 15 minutes at 50°. When upon addition of nitric acid to the compound a reaction occurs in which oxides of nitrogen are evolved, oxidation is likely to have occurred; in such cases it is advisable to cool the reagent and perform the nitration at 0–5°.

The specially prepared acid may be used for dinitration and trinitration by admixing it with concentrated or fuming sulfuric acid.

12.7 p-Nitroiodobenzene. Use 200 mg of iodobenzene, 2 ml of sulfuric acid, and 2 ml of concentrated nitric acid; follow the directions

given in the general procedure described in the preceding section. Heat for 15 minutes at 45–55°. Crystallize the nitration product three times, using 4 ml of hot methanol in the first crystallization and slightly less in the second and third. The crystals melt at the following temperatures: first crystallization, 162–5°; second, 167–9°; and third 170–1°. The yield of the pure product is 40–60 mg.

Note: *p*-Bromochlorobenzene, when nitrated by the same procedure, yields 60–80 mg of the nitro compound, 2-nitro-4-bromochlorobenzene. Three crystallizations are required to obtain a melting point of 71–72°. An alternate method is to mix 50 mg of the halide with 0.1 ml of 100 per cent nitric acid and allow to stand for 15 minutes. About 2 ml of water is added and the crystals separate out; they are then filtered and crystallized once from methanol. About 25 mg of the nitro compound are obtained, melting at 71–72°.

p-Dichlorobenzene and *p*-dibromobenzene nitrate easily; when the same procedure and quantity are employed (12.7), one crystallization is required to obtain the pure nitro compound. *p*-Dichlorobenzene yields 130–150 mg, and *p*-dibromobenzene 100–120 mg of the nitro compound. It should be noted that *p*-dichlorobenzene yields, under the conditions described, a mononitro compound, (2-position), whereas *p*-dibromobenzene yields a dinitro compound (2,5-positions). Unless the compound is reactive, the introduction of two nitro groups requires treatment with fuming nitric acid.

12.8 2,4-Dinitrochlorobenzene. Place in an 8-inch tube 2 ml of concentrated sulfuric acid and 200 mg of chlorobenzene. Cool and add slowly 2 ml of fuming nitric acid. Heat the tube in a bath at 90–100° for 30 minutes and mix the contents by shaking frequently. Cool and add the mixture to 10 ml of water and crystallize as described in Section 12.6 above. Two to three crystallizations are required to obtain a product that melts at 52°. The yield is 100–120 mg.

Note: When fuming nitric acid is used, care should be taken if oxidizable groups are present. If a considerable amount of brown fumes are evolved during nitration, it is advisable to use a lower temperature.

For the preparation of 4-nitrochlorobenzene, mix in a 4-inch test tube 100 mg of the halide and 0.3 ml of 100 per cent nitric acid, and allow to stand at room temperature for 20 minutes. Add 2 ml of water and, after cooling, extract with 2 ml of ether. Draw the ether layer by means of a capillary pipette and place in another tube. Add one pellet of sodium hydroxide and shake gently for a few minutes. Evaporate the ether from a small dish and dissolve the residue in 2 ml of hot methanol. Filter with suction and add water dropwise until a permanent cloudiness results. Cool and filter the crystals. About 50–70 mg of 4-nitrochlorobenzene is obtained; the compound melts at 82–83°.

Selected References on Halogen Compounds

Preparation of anilides, p-toluidides and α-naphthalides. Underwood and Gale, *J. Am. Chem. Soc.*, **56,** 2117 (1934); Schwartz and Johnson, *ibid.*, **53,** 1063 (1931); Gilman and Furry, *ibid.*, **50,** 1214 (1928).

Preparation of alkylmercuric halides. Marvel, Gauerke, and Hill, *J. Am. Chem. Soc.*, **47,** 3009 (1925); Slotta and Jacobi, *J. prakt. Chem.*, **120,** 249 (1929), Hill, *J. Am. Chem. Soc.*, **50,** 167 (1928).

Triiodophenyl ethers as reagents for alkyl halides. Drew and Stutervant, *J. Am. Chem. Soc.*, **61,** 2666 (1939).

Ethers of p-hydrobenzoic acids as derivatives for alkyl halides. Lauer, et al., *J. Am. Chem. Soc.*, **61,** 3050 (1939).

Identification of halides by means of N-alkyl-p-bromobenzenesulfon-p-anisidides. Gillespie, *J. Am. Chem. Soc.*, **56,** 2740 (1934).

Preparation of N-Alkyltetrachlorophthalimides. Allen and Nicholls, *J. Am. Chem. Soc.*, **56,** 1409 (1934).

Preparation of S-Alkyliosothiourea picrates. Brown and Campbell, *J. Chem. Soc.*, **1937,** 1699; Levy and Campbell, *ibid.*, **1939,** 1442

Preparation of alkylsaccharins. Merritt, Levey, and Cutter, *J. Am. Chem. Soc.*, **61,** 15 (1939).

Identification of aryl halides by conversion to sulfonamides. Huntress and Carten, *J. Am. Chem. Soc.*, **52,** 511 (1940).

Preparation of N-alkyl-p-toluenesulfontoluides. Young, *J. Am. Chem. Soc.*, **56,** 2167, 2783 (1934); **57,** 773 (1935).

Use of silver 3,5-dinitrobenzoate for halides. Tsen, *et al., Natl. Central Univ. Sci. Repts., Ser (A), Phys. Sci.*, **1,** 9–14 (1930); *ibid.*, **2,** 7 (1931).

Use of potassium 3-nitrophthalimide for the identification of halides. Sah and Ma, *Ber.*, **65B,** 1930 (1932); *ibid., Science Repts., Natl. Tsing Hua Univ.*, **2,** 147 (1933).

Identification of the halogen in organic halogen compounds. Wilson and Wilson, *J. Chem. Soc.*, **1939,** 1956.

The identification of aryl iodides by means of their iodoso chlorides. Nicol and Sandin, *J. Am. Chem. Soc.*, **67,** 1307 (1937).

Derivatives of Nitro Compounds

The first reaction to be considered in the derivatization of a nitro compound is its reduction to an amine that may be easily identified by conversion to *N-substituted benzamides, acetamides, aryl sulfonamides, and substituted thioureas* (page 253).

The reduction of nitro compounds to amines may be effected either by hydrogenation or by means of tin, zinc, or iron in acid media. The

former method is advisable when the quantity of the nitro compound available is less than 100 mg. The details of this method are given on pages 169–171. Tin and hydrochloric acid are most commonly used for reduction in acid media. After the reduction of the nitro compound, the solution is rendered alkaline and the amine is extracted with ether. If the product is a lower alkylamine, the alkaline solution is distilled, and the distillate is collected in a small amount of dilute acid. The distillate is directly used for the preparation of derivatives by means of acylation.

In the case of aromatic nitro compounds there are often alternative methods for the preparation of derivatives. For example, *p*-nitrotoluene may be reduced to *p*-toluidine, nitrated to 2,4-dinitrotoluene, or oxidized to *p*-nitrobenzoic acid. In general, most aromatic mononitro compounds may be converted to dinitro or trinitro derivatives; in addition, other substituents already present may be altered; for example, the aryl nitro compound may be brominated or an alkyl side chain may be oxidized. The selection of the derivative should be the result of a judicious consideration of all the factors involved. The example of *p*-nitrotoluene may be further considered as an illustration; if *p*-nitrotoluene is reduced to *p*-toluidine, the melting point of the amine is low (45°) and must be acylated for identification. The second alternative is to oxidize *p*-nitrotoluene to *p*-nitrobenzoic acid; the disadvantage of this method lies in the high melting point of the acid. The third alternative, which is selected as a trial, is the preparation of 2,4-dinitrotoluene. The ease of nitration and purification of the dinitro compound as compared with the preparation of other possible derivatives are the factors that suggest this selection.

The derivatization of dinitro, trinitro, and in general polynitro compounds must be considered individually for each compound. Addition compounds of polynitro derivatives often prove desirable derivatives. At least two nitro groups on each benzene ring are required for the formation of addition compounds. The relative position of the nitro groups and the nature of other substituents present in the ring also have an influence on the formation of the addition compound. Nitro groups *ortho* to each other and methyl groups situated between nitro groups appear to hinder addition compound formation. α-Naphthol is stated in the literature as having a greater tendency to form addition compounds than naphthalene; the latter, however, is the reagent recommended because it is easily available in the pure form.

To prepare addition compounds of naphthalene with aromatic polynitro compounds, equimolecular amounts of each are heated cautiously

until a homogeneous melt is obtained. The melt is cooled, recrystallized, from alcohol, dried rapidly, and the melting point determined.

A number of polynitro compounds with substituents other than nitro groups may be derivatized by alteration of their substituents. For example, 2,4-dinitrochlorobenzene may be converted by hydrolysis to 2,4-dinitrophenol; similarly, 2,4,6-trinitroanisole and the 2,4,6-trinitrophenetole may be hydrolyzed to give picric acid. Oxidation of methyl groups is feasible, although such oxidation should be done with *care* even with semimicro quantities; for example, 2,4,6-trinitrotoluene may be converted by oxidation to 2,4,6-trinitrobenzoic acid.

For discussion of the general methods of nitration, the reader is referred to page 284.

12.9 n-Propylamine from 1-nitropropane. Place in an 8-inch test tube 200 mg of 1-nitropropane and 3 ml of 6 *N* hydrochloric acid solution. Add 500 mg of tin in 2 portions over a period of 10 minutes, warming at first to start the reaction. Boil the mixture gently under reflux for 30 minutes or until the odor of the compound has disappeared. Cool the mixture by immersion of the tube in running tap water and add slowly 6 ml of 6 *N* sodium hydroxide. Transfer contents of tube to an 8-inch distilling tube; wash vessel with 1–2 ml of water and unite washings with the alkaline mixture. Add 2 boiling stones and distil the alkaline solution until 4 ml of distillate have been collected in a receiving tube containing 2 ml of 6 *N* hydrochloric acid and 1 drop of aqueous methyl red or methyl orange solution. If the distillate becomes alkaline, a small amount of additional hydrochloric acid is added. Add to the distillate 0.4 ml of benzoyl chloride and then, while the tube is cooled in tap water, 8 ml of 6 *N* sodium hydroxide solution. The tube is stoppered with a solid rubber stopper and shaken vigorously at intervals for 10 minutes. An oil separates out that, on cooling and shaking, solidifies. Then proceed as directed in Section 11.15, page 258. The yield is 30–35 mg of the pure derivative, melting at 84°.

Note: If the amine boils much above 100°, it is best to extract the alkaline solution with ether. In such a case the acid solution that contains the amine salt is made alkaline, care being taken not to use a great excess of alkali; it is then extracted with 3 portions of 4–5 ml of ether (which is free from alcohol), and this extract is used directly for the preparation of the derivative.

12.10 Nitration of o-nitrotoluene and p-nitrotoluene to 2,4-dinitrotoluene. *o*-Nitrotoluene is a liquid, while *p*-nitrotoluene is a solid (*m* 51.9°; 54°); on nitration both yield 2,4-dinitrotoluene. The method

used is described in Section 12.6, page 284. Use 200 mg of the mononitro compound. In the case of *p*-nitrotoluene, after one crystallization 60–70 mg of the pure dinitro compound (m. p. 70°) are obtained. In the case of *o*-nitrotoluene, two crystallizations are required, and the yield of the pure derivative is 40–50 mg.

Selected References on Nitro Compounds

Reduction of nitro compounds by hydrogenation. See Sections 8.6 and 8.10 8.15, pages 166–171.

Identification of polynitro compounds as addition compounds. Asahina and Shinomiya, *J. Chem. Soc. Japan*, **59**, 341 (1938); Dermer and Smith, *J. Am. Chem. Soc.*, **61**, 748 (1939); Sinomiya, *Bull. Soc. Japan*, **15**, 92 (1940).

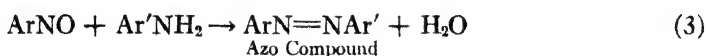
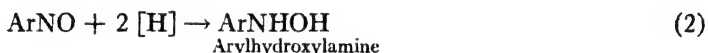
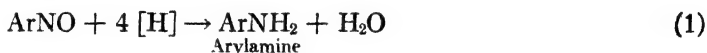
Identification of nitro compounds by catalytic hydrogenation at atmosphere pressure. Cheronis and Koeck, *J. Chem. Educ.*, **20**, 488 (1943); Cheronis and Levin, *ibid.*, **21**, 603 (1944).

Derivatives of Nitroso, Azoxy, Hydrazo and Azo Compounds

Nitroso compounds. The reactions by means of which the nitroso compounds containing C–N linkage may be derivatized are shown in the following equations:

$$ArNO + 4\,[H] \rightarrow \underset{\text{Arylamine}}{ArNH_2} + H_2O \qquad (1)$$

$$ArNO + 2\,[H] \rightarrow \underset{\text{Arylhydroxylamine}}{ArNHOH} \qquad (2)$$

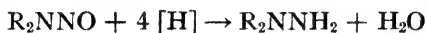
$$ArNO + Ar'NH_2 \rightarrow \underset{\text{Azo Compound}}{ArN{=}NAr'} + H_2O \qquad (3)$$

Equation (1) shows the reduction of the nitroso compound to an *amine*. The reduction may be accomplished either by tin and hydrochloric acid or by catalytic hydrogenation. The latter is to be preferred when the amount available is very small. For discussion on methods of reduction, refer to pages 163–171.

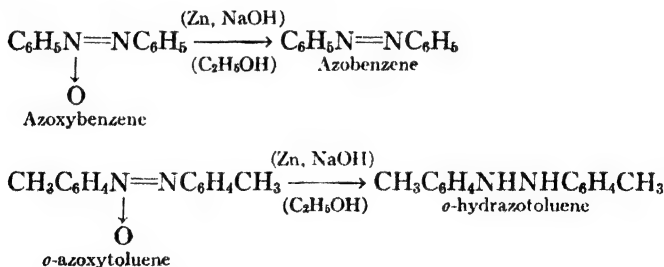
Equation (2) represents the reduction of the nitroso compound to the *hydroxylamine* by means of zinc dust in presence of ammonium chloride or calcium chloride. The nitroso compound is dissolved or suspended in a mixture of alcohol and water, and zinc dust is added, keeping the temperature at 40–50°. The hydroxylamine separates on cooling the hot filtrate of the reaction mixture.

Equation (3) represents the formation of an *azo compound* by the reaction of the nitroso compound with an arylamine. Thus, by addition of aniline to nitrosobenzene, orange-red crystals of azobenzene (m. p. 68°)

are formed. The rate at which the azo compound is formed varies. For example, *p*-iodonitrosobenzene requires several days to react with *p*-aminobenzoic acid to give *p*-iodophenylazobenzoic acid. *p*-Bromoaniline is the most suitable arylamine for reaction with nitroso compounds, giving substituted *p*-bromoazobenzenes.

The nitroso amines, which contain an N–N linkage, are derivatized by reduction to *hydrazines*, which in turn are converted to *hydrazones* through reaction with carbonyl compounds:

$$R_2NNO + 4\,[H] \rightarrow R_2NNH_2 + H_2O$$

The yield of hydrazines by reduction of the nitroamines using semimicro quantities are extremely poor, and hence, if the hydrazine is not obtained on the first trial, it is advisable to use energetic reduction by means of zinc and hydrochloric acid to convert the nitrosoamine to the corresponding secondary amine, which is then derivatized. For example, N-nitrosodiphenylamine, $(C_6H_5)_2NNO$, and di-*n*-butylnitrosoamine fail to give appreciable quantities of the corresponding hydrazines when reduced by means of zinc dust and acetic acid; a further difficulty arises in that many of the derivatives (hydrazones) of the substituted hydrazines are not described in the literature. For these reasons it seems preferable to reduce the nitrosoamine to the corresponding secondary amine and derivatize the latter.

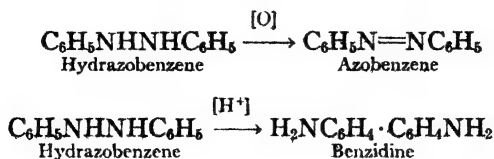
Azoxy and hydrazo compounds. Only a few azoxy and hydrazo compounds are of importance. The azoxy compounds are easily converted by reduction to *hydrazo* or *azo* compounds.

$$\underset{\text{Azoxybenzene}}{C_6H_5\underset{\substack{\downarrow \\ O}}{N}{=}NC_6H_5} \xrightarrow[(C_2H_5OH)]{(Zn,\ NaOH)} \underset{\text{Azobenzene}}{C_6H_5N{=}NC_6H_5}$$

$$\underset{o\text{-azoxytoluene}}{CH_3C_6H_4\underset{\substack{\downarrow \\ O}}{N}{=}NC_6H_4CH_3} \xrightarrow[(C_2H_5OH)]{(Zn,\ NaOH)} \underset{o\text{-hydrazotoluene}}{CH_3C_6H_4NHNHC_6H_4CH_3}$$

The hydrazo compounds may be easily oxidized to azo compounds or often rearranged in acid media to diamino compounds.

$$\underset{\text{Hydrazobenzene}}{C_6H_5NHNHC_6H_5} \xrightarrow{[O]} \underset{\text{Azobenzene}}{C_6H_5N{=}NC_6H_5}$$

$$\underset{\text{Hydrazobenzene}}{C_6H_5NHNHC_6H_5} \xrightarrow{[H^+]} \underset{\text{Benzidine}}{H_2NC_6H_4 \cdot C_6H_4NH_2}$$

In some cases if the hydrazo compound is stable, it may be derivatized by acylation.

Azo compounds. For extensive discussion and systematic identification of azo compounds the reader is referred to treatises on azo dyes. The general reactions by which azo compounds may be derivatized are illustrated by the following equations:

$$\underset{\text{Azobenzene}}{C_6H_5N{=}NC_6H_5} + 2\,[H] \rightarrow \underset{\text{Hydrazobenzene}}{C_6H_5NHNHC_6H_5} \qquad (1)$$

$$C_6H_5N{=}NC_6H_5 + H_2O_2 \rightarrow \underset{\text{Azoxybenzene}}{C_6H_5\underset{\downarrow \atop O}{N}{=}NC_6H_5} + H_2O \qquad (2)$$

$$\underset{\text{Benzeneazo-}\beta\text{-naphthol}}{C_6H_5N{=}NC_{10}H_6(OH)} + (CH_3CO)_2O \rightarrow \underset{\text{Acetyl Benzeneazo-}\beta\text{-naphthol}}{C_6H_5N{=}NC_{10}H_6OCOCH_3} + CH_3COOH \qquad (3)$$

$$C_6H_5N{=}NC_{10}H_6(OH) + 2\,Zn + 6\,HCl \rightarrow C_6H_5NH_3Cl + (OH)C_{10}H_6NH_3Cl + 2\,ZnCl_2 \qquad (4)$$

Equation (1) shows the conversion of azobenzene to hydrazobenzene by mild reduction, while equation (2) represents oxidation by hydrogen peroxide to azoxybenzene. Although both of these methods may be used for a number of azo compounds, the general procedures recommended are illustrated by Equations (3) and (4). If the azo compound contains an amino or hydroxy group, which is the case with most azo dyes, acetylation or benzoylation readily yields a crystalline derivative. A disadvantage to this method arises from the fact that few acyl derivatives of the azo compounds are described in the literature. Therefore the most commonly used method is energetic reduction, as shown in Equation (4). The two amino compounds produced represent: (a) the original amine from which the azo compound was formed by diazotization; (b) the coupling agent, which contains an amino group in the position previously occupied by the azo group. In the example represented by Equation (4), the original amine is aniline and the coupling agent β-naphthol. The hydrochlorides of the two amines may be separated by difference in solubilities; aniline hydrochloride is soluble while the aminonaphthol salt separates out and is filtered. The separation may also be accomplished by steam distillation after the reduction mixture has been made alkaline; aniline, being more volatile, distils with steam.

A general method for the reduction of the azo compounds is to treat 500 mg of the purified substance with 5 ml of a 25 per cent solution of stannous chloride in concentrated hydrochloric acid. The subsequent method of separation of the two amines depends on the nature of the azo

compound reduced. Usually the reduction mixture is cooled and filtered from any precipitate that separates out. The mixture is then made alkaline and steam distilled. The residue in the distilling flask is cooled and extracted with ether. The steam distillate and ether extract are used to prepare derivatives of the two amines.

Azo compounds containing naphthylamine (or naphthylamine sulfonic acids) as the coupling component yield by energetic reduction *o*-diaminonaphthalene. For example, Congo red on reduction yields benzidine and 1,2-diaminonaphthalene-4-sulfonic acid. The *o*-diaminonaphthalene derivatives, when heated with phenanthroquinone, yield characteristic colored compounds (derivatives of quinoxaline).

Selected References on Nitroso Compounds and Azo Dyes

Identification of nitroso compounds by use of p-bromoaniline. Levy and Campbell, *J. Chem. Soc.*, **1939**, 1442.

Identification of the reduction products of azo dyes. Ueno, *Bull. Inst. Phys. Chem. Research* (*Tokyo*), **I**, 4988 (1928); See *C.A.*, **22**, 3999.

Derivatives of Nitriles

The most useful method for the derivatization of nitriles is hydrolysis to the corresponding carboxylic acids; a number of other reactions that may be used for the preparation of derivatives are illustrated in Equations (3) to (7):

$$RCN + H_2SO_4 + 2H_2O \longrightarrow RCOOH + NH_4HSO_4 \qquad (1)$$

$$RCN + NaOH + H_2O \longrightarrow RCOONa + NH_3 \qquad (2)$$

$$RCN + H_2O\ (H_2SO_4) \longrightarrow RCONH_2 \qquad (3)$$

$$RCN + R'MgX \longrightarrow \underset{\displaystyle R'}{\underset{|}{RC}}{=}NMgX \qquad (4)$$

$$\underset{\displaystyle R'}{\underset{|}{RC}}{=}NMgX + 2\,HX + H_2O \longrightarrow RCOR' + NH_4X + MgX_2$$

$$RCOR' + H_2NNHCONH_2 \longrightarrow \underset{\text{Semicarbazone}}{(RR')C{=}NNHCONH_2} + H_2O$$

$$RCN + \underset{\substack{\text{Thioglycolic Acid}\\\text{(Mercaptoacetic Acid)}}}{HSCH_2COOH} + HCl \longrightarrow \underset{\substack{\alpha\text{-Iminoalkylmercaptoacetic Acid}\\\text{Hydrochloride}}}{RC{\left\langle\begin{matrix}{=}NH\cdot HCl\\ SCH_2COOH\end{matrix}\right.}} \qquad (5)$$

$$RCN + C_6H_3(OH)_3 + HCl \xrightarrow{ZnCl_2} (HO)_3C_6H_2C(R){=}NH \cdot HCl \longrightarrow (HO)_3C_6H_2C(R){=}O \tag{6}$$

Alkyl Trihydroxy Phenyl Ketone

$$RCN + 4[H] \longrightarrow RCH_2NH_2 \tag{7}$$

The hydrolysis of the nitriles to *carboxylic acids* may be effected either by heating with acids (Equation 1), or with alkalies (Equation 2). The most common procedure for acid hydrolysis is to heat the nitrile with 75 per cent sulfuric acid at 160–190°. For semimicro quantities a mixture of four parts phosphoric acid (85 per cent) to one part of sulfuric acid (75 per cent) gives better results. If the acid is volatile, or distils below 200° without decomposition, a small amount of water is added after the hydrolysis, and the mixture is distilled; the distillate is used for the preparation of the *p*-nitrobenzyl ester. If the carboxylic acid formed in the hydrolysis is solid, the reaction mixture is diluted with water and carefully treated with sodium hydroxide solution in order to reduce the excess acidity; the solution is then extracted with ether to obtain the solid carboxylic acid.

For alkaline hydrolysis the nitrile is heated with a solution of potassium hydroxide in diethylene glycol or glycerol; if an aqueous solution is used, the heating period should be doubled. After hydrolysis the reaction mixture is carefully acidified, and the carboxylic acid is either distilled or extracted with ether.

Equation (3) represents the hydrolysis of the nitrile to the *amide*. A number of aryl nitriles and hydroxy substituted alkyl nitriles, when treated with a small amount of concentrated sulfuric acid at temperatures ranging from 20 to 80°, undergo partial hydrolysis to form amides. Since the amides are solids, it is easy to determine whether the nitrile under consideration undergoes such hydration; a few drops of the nitrile are placed in a tube and two drops of 95 per cent sulfuric acid are added. The mixture is stirred with a thermometer against the sides of the tube; if there is an immediate reaction, the mixture solidifies instantly. If there is no immediate reaction, the mixture is warmed to 50–60° and

after a few minutes cooled. The reaction mixture is treated with water, rendered slightly alkaline with dilute sodium carbonate, and then filtered to obtain the amide.

Equation (4) represents the addition of a nitrile to a Grignard reagent followed by decomposition and hydrolysis to form a *ketone;* the latter may be converted to the *semicarbazone* as shown by the equation or to other carbonyl derivatives. The Grignard reagent recommended in the literature for this reaction is phenylmagnesium bromide in the ratio of four moles of the Grignard reagent to one of the nitrile.

Equation (5) represents the *thioalcoholysis* of the nitrile in presence of hydrogen chloride to form an analogous compound to the one obtained by treatment of the nitrile with alcohol and hydrogen chloride (imino ester hydrochloride). The nitrile with twice the amount of thioglycolic acid (mercaptoacetic acid) is dissolved in a small amount of dry ether and saturated in the cold with dry hydrogen chloride. The crystals of the derivative that separate on standing are filtered and dried in a vacuum. The decomposition point of the derivative is determined by the standard method used for melting points.

Equation (6) represents the conversion of the nitrile to a *ketone* by means of phloroglucinol in the presence of a condensing agent (Hoesch synthesis). From the point of view of derivatization, this reaction is analogous to the Grignard method of converting the nitrile, RCN, to the ketone RCOR. The nitrile and phloroglucinol are dissolved in dry ether; anhydrous zinc chloride is added and dry hydrogen chloride is passed in for about 30 minutes. The oil that separates from the reaction mixture is taken up with water and the aqueous layer is concentrated by heating. The alkyl trihydroxyphenyl ketone separates out on cooling. The method is applicable to quantities of about 500 mg of the nitrile; however, only six such derivatives have been described.

Equation (7) represents the reduction of the nitrile to a *primary amine.* The nitrile (about 0.01 mole) dissolved in absolute alcohol is treated with metallic sodium; the reaction mixture is acidified and the alcohol is removed by distillation. After the solution is rendered alkaline, the amine is distilled and derivatized by means of phenylisothiocyanate.

12.11 Acid hydrolysis of acetonitrile. Place in an 8-inch distilling tube 4 ml of phosphoric acid (85 per cent), 1 ml of sulfuric acid (75 per cent), and 0.4 ml of acetonitrile. Add 2 boiling stones and attach to the tube a reflux condenser; boil gently for 1 hour. Add 3 ml of water and distil until 3.5 ml of distillate have been collected in an 8-inch tube, which serves as a receiver. Add 1 drop of phenolphthalein and sufficient sodium hydroxide solution (10 per cent) to develop a pink color; then make the

solution just acid to the phenolphthalein test with 2–3 drops of dilute hydrochloric acid. Add 200 mg of *p*-nitrobenzyl bromide and 12–15 ml of methanol so that, when the solution is barely refluxing, it is homogeneous. Reflux for 2 hours. Cool for about 30 minutes and filter the crystalline mass that separates out. Recrystallize from 5 ml of alcohol (see page 212). The yield is 70–90 mg.

Note: When the carboxylic acid is not volatile with steam and boils above 200°, it is separated from the phosphoric-sulfuric acid mixture by extraction; the reaction mixture is first diluted with 3 ml of water, cooled, and partially neutralized with 6 *N* sodium hydroxide solution. It is then extracted with three 5-ml portions of ether. If the acid is solid (from aryl cyanides), the ether is evaporated; otherwise it is used for the preparation of the *p*-toluidide or anilide.

12.12 Alkaline hydrolysis of benzonitrile. Place 4 grams of glycerol, 2 grams of potassium hydroxide pellets, and 0.2 ml of benzonitrile in an 8-inch test tube. (**Caution:** *Care should be used in handling benzonitrile as it is a lachrymator.*) Attach a condenser to the tube and boil gently for 1 hour. Dilute with 1 ml of water, cool, and add 2 ml of ether. Shake gently and allow the immiscible layers to separate. Pour off the ether from the aqueous viscous layer. Cool the tube and make the solution just acid by slow addition of 6 *N* hydrochloric acid solution. Extract three times with 4–5 ml portions of ether. Evaporate the ether in a dish over the steam bath and crystallize the crude benzoic acid by dissolving it in the minimum amount of 90 per cent hot methanol and adding water to the hot solution until a permanent cloudiness results. The yield is 50–70 mg.

Note: The yield of the carboxylic acid from 200 mg of benzonitrile or phenylacetonitrile is usually about 150 mg, but the product melts 2° or more below the melting point of the pure compound. When this method is used with the lower aliphatic nitriles, it is advisable to begin with 400–500 mg of substance.

12.13 Hydrolysis of benzonitrile to benzamide. Use the hood in handling benzonitrile as it has lachrymatory properties. Place 100 mg of this material in a 6-inch tube; rotate the tube in order to distribute the liquid on the lower interior surface. Use a thermometer as a stirring rod; add 5 drops of concentrated sulfuric acid and mix it with the nitrile by means of the thermometer, spreading the mixture over the glass surface. The temperature rises to 40–50°, and the mixture sets into a solid mass. Place the tube in a water bath at 60–70° and allow it to stand for 2–3 minutes with occasional stirring. Then add 1 ml of water and cool.

Remove the thermometer, add 2 ml of sodium carbonate solution (10%), and shake the mixture vigorously so as to dissolve any benzoic acid that may have formed. Filter the crystals of benzamide and wash twice with water; then dry. The yield is 40–50 mg of crystals that melt at 127–128°.

Derivatives of Isocyanides, Isocyanates, and Isothiocyanates

A few of the isocyanides, isocyanates, and isothiocyanates, like phenyl isocyanate and α-naphthyl isocyanate and phenyl isothiocyanate, are among the most common reagents used for the characterization of alcohols, phenols, and amines. The alkyl isocyanides and isocyanates are readily hydrolyzed to the corresponding alkylamines; for example, ethyl isocyanide reacts vigorously at room temperature with concentrated hydrochloric acid to give ethylamine. Likewise, methyl isocyanate is hydrolyzed when boiled with sodium hydroxide solution to methylamine. The hydrolysis of the arylisocyanates to substituted ureas was discussed in the section dealing with the preparation of urethans from alcohols. The arylisothiocyanates may be easily derivatized through reactions with either methylamine or aniline.

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Derivatives of Carbohydrates

Although the sugars undergo a large variety of reactions, their derivatization is a rather difficult matter, particularly when the sample is not pure and contains traces of related compounds; the present discussion, therefore, is limited to the derivatization of pure sugars. The reader is referred to standard works on sugars for their separation and identification in mixtures.

The reactions that are chiefly used in the preparation of derivatives of sugars are summarized by the following equations:

$$\begin{array}{l} H \\ C{=}O \\ \vert \\ HC{-}OH \\ \vert \\ R \end{array} + H_2NNHC_6H_5 \longrightarrow \begin{array}{l} H \\ C{=}NNHC_6H_5 \\ \vert \\ HC{-}OH \\ \vert \\ R \end{array} + H_2O \qquad (1)$$

Hexose — Phenylhydrazine — Hexose phenylhydrazone

$$\begin{array}{l} H \\ C{=}O \\ \vert \\ HC{-}OH \\ \vert \\ R \end{array} + H_2NNHC_6H_4(NO_2) \longrightarrow \begin{array}{l} H \\ C{=}NNHC_6H_4(NO_2) \\ \vert \\ HC{-}OH \\ \vert \\ R \end{array} + H_2O \qquad (2)$$

Hexose — *p* Nitrophenylhydrazine — Hexose *p*-nitrophenylhydrazone

$$\begin{array}{l} H \\ C{=}O \\ \vert \\ HC{-}OH \\ \vert \\ R \end{array} + 3C_6H_5NHNH_2 \longrightarrow \begin{array}{l} H \\ C{=}NNHC_6H_5 \\ \vert \\ C{=}NNHC_6H_5 \\ \vert \\ R \end{array} \begin{array}{l} + 2\,H_2O \\ + NH_3 \\ \\ + C_6H_5NH_2 \\ \\ \\ \end{array} \qquad (3)$$

Hexose — Phenylhydrazine — Hexose osazone

$$\begin{array}{l} H \\ C{=}NNHC_6H_5 \\ \vert \\ C{=}NNHC_6H_5 \\ \vert \\ (HCOH)_3 \\ \vert \\ CH_2OH \end{array} \xrightarrow{Cu^{++}} \begin{array}{l} HC{=}N \\ \vert \qquad \rangle NC_6H_5 \\ C{=}N \\ \vert \\ (HCOH)_3 \\ \vert \\ CH_2OH \end{array} + C_6H_5NH_2 \qquad (4)$$

Phenyl-*D*-glucosazone — Phenyl-*D*-glucosotriazole

$$\begin{array}{l} H \\ C{=}O \\ \vert \\ (HCOH)_4 \\ \vert \\ CH_2OH \end{array} + 5(CH_3CO)_2O \longrightarrow \begin{array}{l} H \\ C{=}O \\ \vert \\ (HC{-}OCOCH_3)_4 \\ \vert \\ CH_2{-}OCOCH_3 \end{array} + 5CH_3COOH \qquad (5)$$

Glucose — Glucose pentaacetate

Equations (1) and (2) represent the formation of *phenylhydrazones* and *substituted phenylhydrazones*. The formation of hydrazones is accomplished by treatment of the sugar with a little more than an equimolecular quantity of phenylhydrazine. The sugar is dissolved in a small quantity of water (100 mg/ml), and the required amount of phenylhydrazine in an equal volume of 50 per cent acetic acid is added; the mixture is allowed to stand for 24 hours in the cold. In the case of substituted phenylhydrazines a small amount of alcohol is used in the reaction mixture; for

example, 100 mg of the sugar dissolved in 1 ml of water are mixed with 100 mg of *p*-nitrophenylhydrazine hydrochloride suspended in 1 ml of methanol. After standing, the hydrazones are filtered, washed with water, and crystallized by first dissolving in the minimum amount of hot methanol or ethanol and then precipitating by the cautious addition of water.

The hydrazones may be reconverted to the original sugar by reacting them with benzaldehyde or formaldehyde; the hydrazone of the aldehyde separates, leaving the sugar in solution. This property and the fact that the hydrazones of the various sugars separate with varying speeds make them useful in the separation of mixtures; the hydrazones are filtered off as they are formed and then are converted to the original sugar by treatment of the hydrazone with an aldehyde.

Among the most important substituted phenylhydrazines used for the preparation of derivatives are *p-nitrophenylhydrazine* (*also the m- and o-isomers*), *p-bromophenylhydrazine*, *methylphenylhydrazine*, *diphenylhydrazine*, *and β-naphthylhydrazine.*

Equation (3) represents the formation of the *osazones* by reacting sugars with excess of hydrazine. The reaction takes place rapidly, as compared with the formation of hydrazones, when a solution of the sugar is warmed with excess of the hydrazine. The mechanism of the reaction is assumed to be, first, the formation of the hydrazone, followed by oxidation of an adjacent carbon atom to the carbonyl stage and subsequent reaction with the hydrazine to produce the osazone. In the preparation of osazones the sugar solution is mixed with a solution of phenylhydrazine acetate, or phenylhydrazine hydrochloride and sodium acetate, in a tube and then heated in boiling water for 30 minutes. The time required for the formation of osazone may be used as additional evidence in the characterization of the unknown sugar, *provided the sample is a pure substance* and not contaminated with small amounts of other sugars. The exact time required for the appearance of the osazone, after the tube is immersed in boiling water, depends on several factors, such as the amount of sugar, reagent, *p*H of the solution, and the amount of solvent. Generally, however, the following descending ease of formation of phenylosazones is observed: *fructose, sorbose, glucose, xylose, rhamnose, arabinose, galactose;* sucrose undergoes hydrolysis and slowly forms (after about 20 minutes) a small amount of the glucosazone. The osazones of maltose and lactose are soluble in the hot solution and separate out only on cooling. It should be again noted that the time of formation of osazone is of value only in the case of pure sugars. The presence of impurities of other osazones greatly influences the rate of crystallization.

The purification of osazones must be undertaken immediately after they have been filtered and washed with cold water. A small amount is kept for the determination of the melting point, and the balance is dissolved in the minimum amount of hot methanol or ethanol and then precipitated cautiously by addition of water. It is not recommended to dry osazones in air. The phenyl-*D*-glucosazone does not show appreciable change when dried in air, but a number of other phenylosazones show extensive reduction of the melting point. For example, in one experiment the osazone from 100 mg of lactose was divided into 3 portions; the sample dried in a watch glass over a water bath gave a melting point of 188–190°; the sample dried in air melted at 191–192°; while the sample dried in a vacuum dessicator melted at 209–210°, which is the value listed in the literature for the pure derivative.

The melting points of the osazones are not to be considered with the same regard as the melting points of other derivatives because the melting points are really decomposition points (see page 39), which vary greatly, depending on the rate of heating. For example, the melting point of phenyl-*D*-glucosazone listed in the literature is 210°. For a given sample of the pure derivative the melting point of 210° will be observed if the rate of heating is 40–60° per minute. If the temperature is raised 8–10° per minute (which is regarded as very rapid in the usual practice near the melting point of a substance), the observed melting point will be below 200° and usually between 194–198°. It is obvious that under these conditions reproducibility of observations requires great care. The osazone of the sugar suspected to be the unknown should always be prepared for comparison.

Another limiting factor in the use of osazones for the characterization of sugars is the fact that a number of isomeric sugars give the same osazone. The following serve as examples: *D*-glucose, *D*-mannose, and *D*-fructose; *D*-arabinose and *D*-ribose; *D*-xylose and *D*-lyxose. In addition, the corresponding sugars of the *L*-series, which have the same configuration beyond the second carbon atom, yield the same osazone, differing from the *D*-osazone only in the direction of the rotation.

Methylphenylhydrazine is useful for differentiating between aldoses and ketoses, which yield the same osazone. For example, *D*-fructose reacts readily with methylphenylhydrazine to form a characteristic osazone, whereas *D*-glucose and *D*-mannose do not.

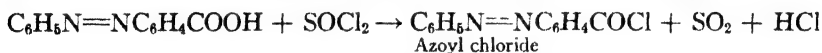
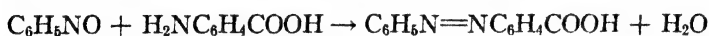
Two important methods have been developed recently that are extremely useful in the identification of sugars. The first is the conversion of the *osazone* to the *osotriazole*[2] as is shown by Equation (4). In this

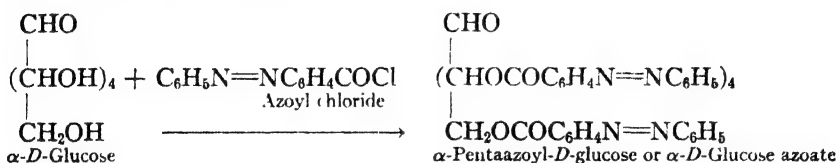
[2] Hann and Hudson, *J. Am. Chem. Soc.*, **66**, 735 (1944); **68**, 1769 (1946).

reaction one of the phenylhydrazine groups is oxidized to aniline with formation of a ring containing 3 nitrogen (triazo) atoms. The ***phenylosotriazoles*** differ from the osazones by their sharp melting points, and hence they are recommended for confirmation of the identity of phenylosazones. The preparation of the phenylosotriazoles from 100 mg of the osazone is feasible, and directions are given in Section 12.18, page 304.

The preparation of *azoates*,[3] although not recommended for the beginner, is an important method for the experienced worker and useful in the identification and separation of sugars. The basis of the method is the preparation of colored esters of the sugars and their separation by chromatographic adsorption. The reagent, *p-phenylazobenzoyl chloride*, commonly called *azoyl* chloride, is prepared by reacting *p*-aminobenzoic acid and nitrosobenzene and then converting the acid to the chloride:

$$C_6H_5NO + H_2NC_6H_4COOH \rightarrow C_6H_5N{=}NC_6H_4COOH + H_2O$$

$$C_6H_5N{=}NC_6H_4COOH + SOCl_2 \rightarrow \underset{\text{Azoyl chloride}}{C_6H_5N{=}NC_6H_4COCl} + SO_2 + HCl$$

The azoyl chloride reacts slowly in pyridine solution with the hydroxyl groups of the sugar to form the *azoates:*

$$\underset{\alpha\text{-}D\text{-Glucose}}{\begin{array}{l} CHO \\ | \\ (CHOH)_4 \\ | \\ CH_2OH \end{array}} + \underset{\text{Azoyl chloride}}{C_6H_5N{=}NC_6H_4COCl} \longrightarrow \underset{\alpha\text{-Pentaazoyl-}D\text{-glucose or }\alpha\text{-}D\text{-Glucose azoate}}{\begin{array}{l} CHO \\ | \\ (CHOCOC_6H_4N{=}NC_6H_5)_4 \\ | \\ CH_2OCOC_6H_4N{=}NC_6H_5 \end{array}}$$

The *azoates* are colored from orange to dark red and are adsorbed from their solutions in organic solvents by many of the adsorbents commonly employed for chromatographic adsorption, such as silicic acid, Magnesol, and Diccalite (page 340).

The preparation of azoates is very useful in the systematic work of sugars, although it may not be widely applicable to routine work, since the length of time required for the reaction of azoyl chloride with sugars is 8 to 10 days.

The optical activity of osazones, hydrazones, and azoates is employed sometimes as a means of identification. The rotation must be measured under specified conditions as to quantity of material and nature of solvent. For osazones a mixture of 40 per cent pyridine and 60 per cent alcohol is commonly used as a solvent; for azoates, alcohol-free chloroform is employed. The derivative must be of high purity. Special methods of purification are necessary when the original sample is an im-

[3] Coleman and McClosky, *ibid.*, **64**, 1501 (1942); **65**, 1588 (1943); Reich, *Biochem. J.*, **33**, 1000 (1939).

pure sugar. For example, glutose, for a long time, was considered a ketohexose sugar, that yielded a phenylosazone melting at 163–165°. Recently it has been shown[4] to be a fructose anhydride mixture. The phenylosazone, which melts at 163–165°, is a mixture of glucosazone and of the osazone of methylglyoxal and may be recrystallized from alcohol and other osazone solvents without change in its melting point. When it is treated with dry acetone, the osazone of methylglyoxal dissolves, leaving the pure glucosazone. Therefore, it is recommended[5] that osazones prepared from impure sugars be washed with acetone before final purification.

The conversion of sugars to *acetates*, although relatively easy, is not recommended for the preparation of derivatives for identification work. Aside from difficulties encountered in crystallization, α and β forms are possible in most cases. For example, *D*-glucose treated with acetic anhydride in the presence of anhydrous zinc chloride forms the α-pentaacetate and in the presence of sodium acetate yields the β-form. A recently proposed method[6] for the characterization of the monosaccharides involves oxidation of the sugar by potassium hypoiodite in methanol to the aldonic acid; the latter is condensed with *o*-phenylenediamine to yield benzimidazoles (page 208). Another method proposed for the identification of sugars and the osazones derived from them is by microscopical examination; the reader is referred to a number of excellent articles in the literature, which are listed in the Bibliography.

The oxidation of galactose to mucic acid may be used as a characterization for this sugar and also of lactose and polysaccharides, which yield galactose as one of the hydrolytic products. Mucic acid, $HOOC(CHOH)_4COOH$, is sparingly soluble in water and may be readily identified by its melting point.

The polysaccharides, such as starches and celluloses, are characterized, first, by means of color reactions and physical constants, and second, through the products that they yield on hydrolysis. This fact also applies to the ever-increasing number of cellulose derivatives, such as cellulose acetate, ethyl cellulose, and other esters and ethers of the celluloses.

12.14 Glucose p-nitrophenylhydrazone. Place in a 6-inch tube 100 mg of *p*-nitrophenylhydrazine hydrochloride and 1 ml of methanol; shake

[4] Sattler and Zerban, *Sugar*, **39**, 12 (1944).
[5] Sattler, private communication.
[6] Link et al., *J. Biol. Chem.*, **150**, 345 (1943); *ibid.*, **133**, 293 (1940); *J. Org. Chem.*, **5**, 639 (1940).

for a few seconds and then add 100 mg of glucose, 150 mg of powdered sodium acetate, and 1 ml of water. Cork tube and shake gently so as to mix its contents; allow to stand overnight. Add 2 ml of water and filter the crystals; wash with water and crystallize from 5 ml of 95 per cent ethanol. The yield is 125 mg of crystals, which melt at 189–190°.

Note: The ease of hydrazone formation varies; fructose, under the condition described above, yields an impure hydrazone; it is necessary to allow the mixture to stand for 48 hours and to use slight excess of the sugar in order to obtain satisfactory results. On the other hand, fructose yields the methylphenylhydrazone with great ease as compared with glucose.

12.15 Rate of osazone formation. Place 100 mg of the sugar, 100 mg of sodium acetate, and 2 ml of water in a 6-inch tube. Add 5–6 drops (0.2 g) of phenylhydrazine and 6–7 drops (0.12 g) of glacial acetic acid. Close the tube loosely with a cork and set it in a 600-ml beaker half-filled with water that is already boiling. Note the time required for the appearance of the osazone. When the sample of sugar is pure, the following intervals of time (in minutes) are observed as measured from the moment the tube is immersed in the boiling water to the appearance of the osazone: mannose, 0.5–1; fructose, 1–2; glucose, 4–5; xylose, 6–8; arabinose, 9–10; galactose, 14–16; sucrose, 20–30 (by hydrolysis); and lactose and maltose, on cooling.

Note: Phenylhydrazine hydrochloride may be used in place of the base; in such a case, for 100 mg of sugar use 200 mg of phenylhydrazine hydrochloride, 300 mg of sodium acetate, and 2 ml of water. On standing the salt undergoes decomposition and darkens. It may be purified by crystallization from hot water; the salt is dissolved in the minimum amount of boiling water; the tarry impurities remain undissolved. A small amount of charcoal is added, and the hot solution is filtered rapidly. The solution is cooled, and concentrated hydrochloric acid is added so that the volume of the solution increases by one-third. After an hour the cold mixture is filtered, and the crystals are washed with ice-water and dried.

12.16 Phenyl-D-glucosazone. Place in an 8-inch tube 100 mg of glucose, 100 mg of sodium acetate, 6 drops (0.21 g) of phenylhydrazine, 2 ml of water, and 7 drops (0.13 g) of glacial acetic acid. Immerse the tube in boiling water for 30 minutes. Add 5 ml of water and cool. Filter with suction and wash the tube and crystals—first with 2 ml of water to which 2 drops of acetic acid have been added and then twice with 3 ml of water. Remove a small amount of the osazone and dry in a vacuum desiccator. Transfer the rest of the crystals to the reaction tube and add 20 ml of methanol. Heat to boiling, adding more alcohol

until practically all the osazone has dissolved. Filter and add 2–3 ml of water to the filtrate and cool in an ice-water mixture. Filter the crystals and wash twice with 2 ml of 25 per cent methanol. Dry in a vacuum desiccator. The yield is 90–100 mg. The melting point of the crystals, when determined by the capillary method in an oil bath with a temperature rise of 40–60° per minute, is 209–210° (corrected). The unrecrystallized material usually melts at 207–208°. The identity of phenyl-*D*-glucosazone is confirmed by conversion to the glucosotriazole as directed in Procedure 12.18 below.

Note: Fructose yields the same osazone but with greater ease and a slightly better yield. Some authors recommend the use of pyridine in conjunction with alcohol for crystallization of the osazone. No advantage has been found for this solvent-pair. When the osazone is required for determination of the optical rotation, it should be washed with acetone before crystallization. This operation is best accomplished just before the osazone is removed from the filter funnel for crystallization. About 2–3 ml of acetone are added to the crystals, and after a minute suction is applied and the washing repeated.

Many of the osazones can be identified by microscopical examination of the crystals. The original article cited in the bibliography section should be consulted.

12.17 Lactose phenylosazone. Use the same quantities as in the preparation of glucosazone. Immerse the tube for 20 minutes in boiling water and then add 2 ml of water and cool in an ice-water mixture for 30 minutes. Filter and wash first with 2 ml of water containing 1–2 drops of acetic acid and then twice with 2 ml of cold water. Remove a small portion to a watch glass and place immediately in a vacuum desiccator. Recrystallize the balance from a mixture of 2 ml of water and 1 ml of methanol. After the mixture is brought to boiling, a small amount of charcoal is added and the mixture filtered by suction. The hot solution is cooled in an ice-water mixture for 1 hour, and then the crystals are filtered, washed with two 0.5 ml portions of water, and placed at once in a vacuum desiccator. The yield is 40–45 mg of crystals, which have a melting point of 210–211°.

12.18 Phenyl-D-glucosotriazole. Place 90–100 mg of glucosazone in an 8-inch tube; add 9 ml of water, 2 drops of 6 *N* sulfuric acid, 300 mg of copper sulfate (pentahydrate), 6 ml of isopropyl alcohol, and 2 boiling stones. The mixture is boiled for 1 hour under reflux. The yellowish-green solution is poured into an evaporating dish and concentrated over a water bath to a volume of 3–4 ml. Cool the dish in ice-water and filter the granular crystals; dissolve the crude material in 12–14 ml of boiling

water; add charcoal and filter. Cool the solution overnight in an ice-box. Filter the derivative and wash twice with 1 ml of water. The yield is 16–18 mg of crystals, melting at 193–194°. To crystallize the glucosotriazole, place the crystals in a 6-inch tube; add 1 ml of 95 per cent ethanol and heat to boiling. Add 1 ml of water to the clear solution and cool for 2 hours in an ice-salt mixture. Filter the crystals and wash with 0.5 ml of water. The yield is 13–14 mg of crystals, melting at 195–196°.

12.19 Sucrose octaacetate. Place 200 mg of sodium acetate in a 6-inch tube. Heat over a free flame until all the water has been expelled and the substance is liquid; it is necessary to heat the upper sides of the tube to insure complete removal of the water. Cork the tube and allow to cool. Add 3 ml of acetic anhydride and heat until the solid has dissolved; then add 200 mg of sucrose. Heat for 1–1.5 hours in a water bath at 90–100°. Add 10 ml of water and 1.5 ml of 10 per cent sodium hydroxide solution; place tube in a cold bath and allow to stand overnight. From time to time scratch the inner sides of the tube to induce crystallization of the oil that is separating out. Filter the crystals, place aside a small quantity for determination of the melting point, and recrystallize the balance 3 or 4 times until the melting point remains constant. The first crystals melt at 80–85°, and on successive crystallizations the melting point reaches the value of 75°. For crystallization the octaacetate is dissolved in the minimum amount of boiling alcohol, and then water is added until a permanent cloudiness results. If an oil separates out that does not crystallize on cooling, the mixture is seeded with a minute crystal from the material set aside. Several hours of cooling are required for complete crystallization.

12.20 Mucic acid from galactose and lactose. On a watch glass, which is placed on a steam bath, add 100 mg of lactose or galactose, 1 ml of water, and 0.5 ml (15 drops) of concentrated nitric acid; evaporate the mixture to dryness. By means of a microspatula scrape the residue and transfer into a test tube; wash the watch glass with 2 ml of water and add the washings to the residue in the tube. Heat the mixture to boiling and then cool in an ice-water mixture. Filter the crystalline mass and wash three times with 1 ml of water. Dry the crystals on a watch glass over a steam bath. The yield is 60–70 mg.

Note: The melting point of mucic acid listed in the literature is 214°. Since the compound melts with decomposition, it is not unlikely to obtain values that vary between 210 and 224, depending on the rate of heating. Values near 214° are obtained when the heating is very slow.

Selected References on Carbohydrates

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CHAPTER 13

Preparation of Derivatives—Continued

Derivatives of Hydrocarbons

PARAFFINS and cycloparaffins do not form derivatives useful for characterization work. Although most of the hydrocarbons undergo a variety of reactions under appropriate conditions, the large number of isomers formed and the difficulties involved in the separation of these isomers render such reactions useless for derivatization. For instance, *n*-hexane can be easily brominated; the three monobromo derivatives cannot be easily separated in a state of purity so that they may be used further for the preparation of solid derivatives. A hydrocarbon with a tertiary hydrogen atom may yield a greater proportion of a particular monohalide, but even in such instances other isomers are formed.

Halogenation and oxidation may be used in the characterization of certain cycloparaffins. For example, cyclohexane may be oxidized by hot nitric acid to adipic acid; the chlorination or bromination of cyclohexane may be controlled so as to produce mostly the monohalide, which in turn may be derivatized.

From the above considerations it is evident that the characterization of paraffins and cycloparaffins must be based almost exclusively on the physical constants, particularly on the boiling point, density, and refractive index. These constants in the case of pure compounds lead to fairly accurate results; impurities, particularly those due to isomers, render accurate characterization extremely difficult. In recent years other physical measurements, such as absorption spectra and magnetic rotation, have been used for the identification of hydrocarbons. The reader is referred to the literature cited for description of these methods.

In the analysis of many commercial products, such as paints, varnishes, lacquers, and the like, the primary objective is the characterization of the class of hydrocarbons used as a solvent rather than the identification of individual compounds. The solvent is separated by distillation and is fractionated. Each fraction is then tested by sulfonation or nitration for the presence of aromatic hydrocarbons. On the basis of these tests and the physical properties of the various fractions, it is possible to arrive at a fairly accurate conclusion as to the nature of each. Assume, for example, that 6.5 g of solvent were obtained from the distillation of 10 g

of a particular commercial product. The 6.5 g of sample on fractionation gave the following fractions: I. 130–145°, 1.5 g; II. 145–185°, 0.8 g; III. 185–200°, 2.9 g; IV. 200–210°, 0.8 g. Tests for the presence of aromatic hydrocarbons are positive for fractions I and II and negative for fractions III and IV. Nitration of 0.2 ml from each fraction I and II gives an appreciable amount of nitro compounds from the former but very little from the latter; the nitration product from both fractions after four crystallizations fails to give a constant melting point. The density of fraction I is 0.875 and of fraction III 0.772. From these data, after referring to standard works on commercially available solvents, it is possible to arrive at the conclusion that the 6.5 g of distillate consists of about one third aromatic hydrocarbons and two thirds of paraffinic or cyrloparaffinic hydrocarbons. Reference to the properties of fraction I indicates that it consists of commercial xylene, which is a mixture of the three xylenes. Fractions III and IV are most likely a petroleum distillation product, known commercially as "mineral spirits."

Aromatic hydrocarbons. The nitration of aromatic hydrocarbons is one of the first reactions to be used for the preparation of crystalline derivatives; the formation of dinitro and trinitro derivatives is preferred, as these are less likely to be contaminated by isomers than the mononitro compounds. The nitration mixture usually consists of two volumes of concentrated sulfuric acid and one volume of either concentrated nitric acid or fuming nitric acid; however, the composition of the nitrating mixture as well as the conditions influence the composition of the nitration product. This is shown in Table VI, which summarizes a series of nitration experiments using semimicro quantities of *toluene*, *o-xylene*, *m-xylene*, *p-xylene*, and *isopropylbenzene.* The results indicate that, in order to obtain a product that is likely, after two or three crystallizations, to show the desired melting point, it is necessary to alter the conditions for each of the hydrocarbons.

Inspection of Table VI with reference to the products obtained by the nitration of *m*-xylene indicates that the 2,4-dinitro-*m*-xylene is not easily obtained, but by using fuming nitric acid (series A and D), a product is obtained melting at 176°. Reference to the tables shows that 2,4,6-trinitro-*m*-xylene melts at 183° (180). Therefore, the trinitro derivative is selected. It will be noted that *o*-xylene gives consistently an oil, indicating that even under conditions which cause trinitration on *m*-, and *p*-xylene, it undergoes only mononitration. The oily product can be shown to have a melting point between 8° and 12°, being a mixture of 3-nitro-1,2-dimethylbenzene, melting at 15°, and 4-nitro-1,2-dimethylbenzene melting at 30°. Reference to the literature on the nitration of

o-xylene discloses that in the cold, with fuming nitric acid, the chief products are 3-nitro and 4-nitro in the ratio of 8 to 1. With increasing temperature and an excess of nitric acid the following dinitro derivatives are formed: 3,4-m.p. 82°; 3,5-m.p. 76°; 3,6-m.p. 90° and 4,5-m.p. 118°. From these considerations it is obvious that the best procedure is to nitrate with 100 per cent nitric acid (page 285) at 0°, reduce the product

TABLE VI

Nitration of Some Aromatic Hydrocarbons

Series[1]	Hydrocarbon	Desired Nitration Product		Product	Obtained
		Position	*M. P.*	*M. P.*	*Amount (Mg.)*
A[2]	Toluene	2, 4	70	69–70	120
	o-xylene	4, 5	118	33–40	140
	m-xylene	2, 4	83	176	150
	p-xylene	2, 3, 5	137	74	120
	Isopropylbenzene	2, 4, 6	109	oil	—
B[3]	*o*-xylene	4, 5	118	oil	—
	m-xylene	2, 4	83	58	70
	p-xylene	2, 3, 5	137	88	110
	Isopropylbenzene	2, 4, 6	109	oil	—
C[4]	*o*-xylene	4, 5	118	oil	—
	m-xylene	2, 4	83	72	116
	p-xylene	2, 3, 5	137	78	75
	Isopropylbenzene	2, 4, 6	109	oil	—
D[5]	*o*-xylene	4, 5	118	oil	—
	m-xylene	2, 4	83	176	135
	p-xylene	2, 3, 5	137	136	85
	Isopropylbenzene	2, 4, 6	109	oil	—
E[6]	*o*-xylene	4, 5	118	46–50	105
	Isopropylbenzene	2, 4, 6	109	oil	

[1] In all experiments 200 mg of the hydrocarbon in an 8-inch test tube were treated with the nitrating mixture at the conditions specified in each series The reaction mixture was then poured in 10 g of ice, and any crystalline product that separated was filtered. The crystals were purified by two crystallizations from methanol and the melting point determined

[2] Nitrating mixture: conc. H_2SO_4 1.5 ml; fuming HNO_3 1 5 ml; the mixture was heated for 15 minutes at 60°.

[3] Nitrating mixture: 3 ml of equal volumes of each conc. H_2SO_4 and HNO_3. The mixture was shaken for 5 minutes; no heating except heat of reaction.

[4] Nitrating mixture: 3 ml of conc. H_2SO_4 and 1.5 ml conc. HNO_3; the mixture was shaken for 5 minutes; no heating except heat of reaction.

[5] Nitration mixture: 3 ml of conc. H_2SO_4; 1.5 ml fuming HNO_3; after addition of hydrocarbon, the mixture was shaken for 2 minutes and then heated in a water bath at 70–80° for 15 minutes.

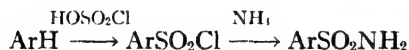
[6] Same as in (5) except that the mixture was heated for 45 minutes.

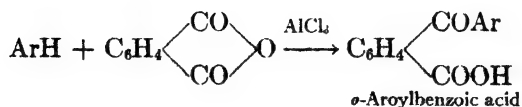
by catalytic hydrogrenation and separate the 3-amino-1,2-dimethylbenzene from the small amount of the 4-amino isomer.

Isopropylbenzene and other monoalkybenzenes do not yield solid nitro derivatives with ease. It will be observed, by inspection of Series E in Table VI, that, after heating isopropylbenzene with a mixture of concentrated sulfuric and fuming nitric acid at 70–80° for 45 minutes, the product is an oil; this oil contains a considerable amount of the dinitro derivative and may be used for characterization by reduction and subsequent conversion to the diacetamino derivative. The method developed by Ipatieff and his collaborators is applicable to the identification of monoalkylbenzenes. The nitration is effected by the methods described in Table VI, Series B and Series C. Under the condition described in Series B, relatively pure *4-nitroalkylbenzenes* are formed with very little of the *ortho*-substituted isomers. With the more vigorous nitrating conditions described in Series C, 2,4-dinitroalkylbenzenes are formed. The nitro derivatives are extracted with ether and are reduced by means of tin and hydrochloric acid to the corresponding amines, which are acetylated to obtain the *4-acetamino* and *2,4-diacetaminoalkylbenzenes.* The first are more suitable for the characterization of the pure hydrocarbons; the second for the components of aromatic mixtures.

Monoalkylbenzenes are oxidized by permanganate to benzoic acid and the dialkylbenzenes to one of the phthalic acids. Although this method is applicable to toluene and the three xylenes, it cannot be used for other alkylbenzenes, since it does not give information as to the nature of the alkyl groups.

Another reaction that may be used with certain hydrocarbons for the preparation of suitable derivatives is *chlorosulfonylation*, followed by ammonolysis of the sulfonyl chloride to the sulfonamide:

$$ArH \xrightarrow{HOSO_2Cl} ArSO_2Cl \xrightarrow{NH_3} ArSO_2NH_2$$

The preparation of aroylbenzoic acids by the condensation of phthalic anhydride with the hydrocarbon in presence of aluminum trichloride (Friedel-Crafts reaction) has been applied to the characterization of about 20 aromatic hydrocarbons:

$$ArH + C_6H_4\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle O \xrightarrow{AlCl_3} \underset{o\text{-Aroylbenzoic acid}}{C_6H_4\left\langle\begin{matrix}COAr\\COOH\end{matrix}\right.}$$

This method is recommended for the hydrocarbons that do not give good results by nitration or nitration followed by reduction and acetylation.

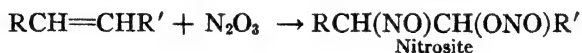
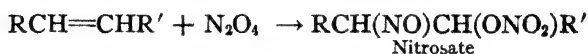
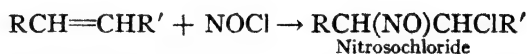
A large number of hydrocarbons react with picric acid and other

trinitro compounds to form addition products; however, only a few of these addition compounds may be isolated in the pure form for determination of melting points. In order that a picrate may be useful in characterization work, it should form when the hydrocarbon is added to an alcoholic or benzene solution of picric acid and be sufficiently stable to be filtered and dried rapidly in air. When these conditions are used, the following results are obtained [the first figure represents the melting point obtained, and the second (in parenthesis) the melting point listed in the literature]: naphthalene, 148 (149); anthracene, 135 (138); phenanthrene, 97–99 (144); β-methylnaphthalene, 91–96 (116); α-methylnaphthalene, 101 (140). In general, it is recommended that the beginner use only the picrates of naphthalene and anthracene for characterization work. For the identification of polynuclear hydrocarbons the use of molecular complexes formed with 2,4,7-trinitrofluorenone is recommended. Besides the ease of formation and purification these molecular complexes melt sharply without decomposition; for details, the original article should be consulted.

Unsaturated hydrocarbons. Although unsaturated hydrocarbons undergo a large number of reactions, there is no simple general method for converting them into solid derivatives suitable for characterization work. A number of unsaturated hydrocarbons, particularly terpenes, may be characterized by the addition of *nitrosyl chloride, nitrogen trioxide*, and *nitrogen tetroxide*.

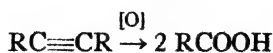
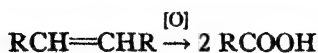
$$RCH{=}CHR' + NOCl \rightarrow \underset{\text{Nitrosochloride}}{RCH(NO)CHClR'}$$

$$RCH{=}CHR' + N_2O_4 \rightarrow \underset{\text{Nitrosate}}{RCH(NO)CH(ONO_2)R'}$$

$$RCH{=}CHR' + N_2O_3 \rightarrow \underset{\text{Nitrosite}}{RCH(NO)CH(ONO)R'}$$

The nitrosochlorides are generally prepared by addition of concentrated hydrochloric acid to a mixture of the hydrocarbon and ethyl nitrite dissolved in acetic acid. The reader is referred to the literature for details on the preparation of these derivatives for the characterization of terpenes.

Unsaturated compounds on oxidation yield carboxylic acids:

$$RCH{=}CHR \xrightarrow{[O]} 2\ RCOOH$$

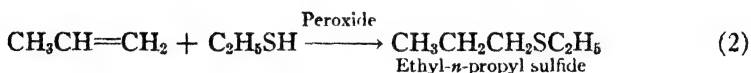
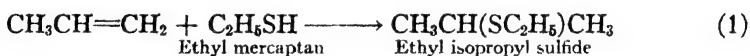
$$RC{\equiv}CR \xrightarrow{[O]} 2\ RCOOH$$

A number of symmetrical olefins or acetylenes (or 1-alkenes and 1-alkynes) that yield predominantly one type of solid carboxylic acid may

be identified by this method. The olefin is either shaken or refluxed with alkaline permanganate. The manganese dioxide is filtered and the alkaline solution is concentrated, acidified, and extracted with ether. If difficulty is encountered in the filtration of manganese dioxide, the solution is concentrated and then sodium bisulfite and dilute hydrochloric acid are added until the solution is clear; it is then cooled and extracted with ether. The difficulty in the application of this method to semimicro quantities arises from the fact that in most cases the oxidation proceeds further than represented by the equations and gives rise to small amounts of other carboxylic acids. For this reason several crystallizations are required to obtain a pure product, and, since the yield of the expected carboxylic acid is usually 50-70 per cent of theory, it is not recommended to start with less than 500 mg of hydrocarbon.

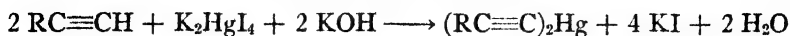
Addition of bromine to unsaturated compounds may be used for characterization if the resulting dibromides are solid. For example, styrene is readily derivatized by the preparation of styrene dibromide. The addition of thiocyanogen to form *dithiocyanates* has been used for the derivatization of ethylene, cyclohexene, 3-methyl-1-cyclohexene, and styrene. Since three of these hydrocarbons may be readily characterized by other derivatives and the handling of thiocyanogen and dithiocyanates involves care, this method is not recommended for beginners.

The addition of *mercaptans* (*thiols*), *thiophenols*, and *thioacids* has been proposed as a means of identification of olefins. The addition to unsymmetrical olefins may take place in two ways, depending on the presence or absence of peroxides and other catalysts:

$$\underset{}{CH_3CH{=}CH_2} + \underset{\text{Ethyl mercaptan}}{C_2H_5SH} \longrightarrow \underset{\text{Ethyl isopropyl sulfide}}{CH_3CH(SC_2H_5)CH_3} \quad (1)$$

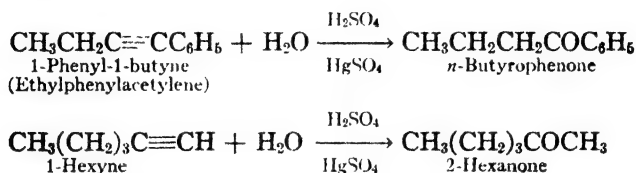
$$CH_3CH{=}CH_2 + C_2H_5SH \xrightarrow{\text{Peroxide}} \underset{\text{Ethyl-}n\text{-propyl sulfide}}{CH_3CH_2CH_2SC_2H_5} \quad (2)$$

Equation (1) shows addition according to Markownikoff's rule; most aliphatic mercaptans and thiophenols add to unsymmetrical olefins according to Equation (2). This method suffers from two disadvantages: first, if the reaction is run at room temperature, several weeks are required for completion; or the reaction may be run at 180° by heating in a bomb for ten hours. Second, most of the thioethers obtained by such reactions are liquids and must be derivatized either by oxidation to sulfones or by preparation of addition compounds with mercuric chloride or palladous chloride.

The monosubstituted acetylenes, $RC{\equiv}CH$, react with an alkaline solution of mercuric iodide or cyanide to give simple mercuric salts:

$$2\,RC{\equiv}CH + K_2HgI_4 + 2\,KOH \longrightarrow (RC{\equiv}C)_2Hg + 4\,KI + 2\,H_2O$$

The acetylene salts are prepared by adding a dilute solution of alkaline mercuric iodide to an alcoholic solution of the acetylene; the acetylene mercuric salt separates immediately. The product is filtered, washed with alcohol, and then crystallized from alcohol or benzene.

Disubstituted acetylenes and some monoalkylacetylenes, such as 1-hexyne, 1-heptyne, and 1-octyne, may be converted to the corresponding ketones by catalytic hydration:

$$\underset{\substack{\text{1-Phenyl-1-butyne}\\\text{(Ethylphenylacetylene)}}}{CH_3CH_2C{\equiv}CC_6H_5} + H_2O \xrightarrow[HgSO_4]{H_2SO_4} \underset{n\text{-Butyrophenone}}{CH_3CH_2CH_2COC_6H_5}$$

$$\underset{\text{1-Hexyne}}{CH_3(CH_2)_3C{\equiv}CH} + H_2O \xrightarrow[HgSO_4]{H_2SO_4} \underset{\text{2-Hexanone}}{CH_3(CH_2)_3COCH_3}$$

The hydration of the alkynes is effected by shaking the hydrocarbon with an alcoholic or aqueous alcoholic solution of sulfuric acid and mercuric sulfate. The mixture may be warmed to complete the reaction, cooled, and diluted with water. If the ketone is a solid, it separates on cooling. If the ketone is a liquid, the ketone is separated either by fractional distillation or by extraction with ether.

Dienes with conjugated double bonds may be derivatized by condensing the hydrocarbon with *maleic anhydride* or *α-naphthoquinone.*

13.1 Oxidation of cyclohexane to adipic acid. Place 2 ml of concentrated nitric acid in an 8-inch test tube and add 1–2 boiling stones. Clamp the tube to a stand in the hood and heat the acid to boiling. Reduce the flame of the microburner and, by means of a dropper, add cautiously 2 drops of cyclohexane; shake the tube and, when the vigorous reaction has subsided, repeat the addition. Add a total 0.2 ml (8–10 drops) of hydrocarbon over a period of 10 minutes. Boil gently for 1 minute and cool. Filter the crystals of adipic acid. Recrystallize from 2–3 ml of boiling water. The yield is 70–80 mg, melting at 152–153°.

13.2 Nitration of toluene. Place in an 8-inch test tube 1.5 ml of concentrated sulfuric acid and 0.25 ml of toluene. Cool and add slowly 1.5 ml of fuming nitric acid. Heat in a water bath for 15 minutes. Remove the tube from the bath every few minutes and shake in order to mix the two layers. Cool and then add 7–8 ml of cold water or the same amount of ice. Filter the solid and wash twice with 2–3 ml of water. Dissolve in 4 ml of hot methanol, filter with suction, and add 1–2 drops of water to the filtrate. Cool for 10 minutes, filter the solid, and repeat the crystallization. The yield is 110–140 mg of 2,4-dinitrotoluene, melting at 69–70°.

Note: As stated under the discussion of aromatic hydrocarbons, the procedure outlined above will not be successful for the nitration of the three xylenes. It is recommended that the entire discussion on nitration (pages 284 and 308) should be read before nitration of an aromatic hydrocarbon is attempted.

13.3 Nitration of m-xylene. Mix in an 8-inch test tube 3 ml of concentrated sulfuric and 1.5 ml of fuming nitric acid. Add 0.25 ml of *m*-xylene. Stopper the tube with a solid rubber stopper and shake for 2–3 minutes; at first heat is generated by the reaction, but the tube should not be immersed in cold water. Let it stand for 2 minutes and then heat in a water bath at 70–80° for 15 minutes. Add 8 ml of cold water and allow the oil that first separates out to crystallize. Filter the solid, wash with water, and recrystallize from 5–6 ml of methanol; repeat crystallization twice, using slightly less solvent for the second and third crystallization. The yield is 100–110 mg of 2,4,6-trinitro-*m*-xylene, melting at 181–2°.

Note: For the preparation of the mononitro derivatives of the alkylbenzenes, see the original article by Ipatieff and Schnerling; the method given on pages 284 and 309 will also be found useful.

13.4 Nitration of p-xylene. Mix 2 ml of concentrated sulfuric acid and 2 ml of fuming nitric acid in an 8-inch test tube. Add 0.2 ml of *p*-xylene and immerse for 30 minutes in a water bath at 90–95°, shaking the tube frequently. Cool and add 20 ml of water. Filter the solid and recrystallize twice from 7–8 ml of methanol. After the hot alcoholic solution has been filtered, about 1 ml of water is added with shaking. The filtrate should be cooled for 10 minutes before the crystals are removed. The yield is 100–120 mg of 2,3,5-trinitro-*p*-xylene, melting at 136°.

13.5 T.N.F. Molecular complex of anthracene. Dissolve 100 mg. of T.N.F. (2,4,7-trinotrofluorenone), in a mixture of 10 ml absolute methanol or ethanol and 2 ml benzene. Boil for a few seconds and add a solution of 60 mg anthracene in 3.5 ml methanol and 1.5 ml benzene. Heat for 30 seconds and cool. Filter the red flocculent crystals, wash with 1 ml methanol, and dry. The yield is 50–60 mg melting at 192–3°. The complex may be recrystallized from absolute alcohol or alcohol-benzene.

13.6 Preparation of p-acetamino derivative of isopropylbenzene. Place in an 8-inch test tube 3 ml of nitrating mixture, consisting of equal volumes of concentrated sulfuric and nitric acids. Add 0.25 ml of isopropylbenzene and shake the mixture in the tube for 5 minutes. Add 8 ml of water and extract with 5 ml of ether. Separate the ether layer

and place in an evaporating dish. When the solvent has evaporated, transfer the remaining oil by means of 1.5 ml methanol in an 8-inch tube. Add 2 ml of concentrated hydrochloric acid and 2 g of tin. Boil gently until practically all the tin dissolves. Cool and dilute with 5 ml of water; add 8 ml of 6 *N* sodium hydroxide solution and then extract with ether. Add to the ether solution 0.5 ml of acetic anhydride and then evaporate the solvent; heat the residue over a small free flame for 1–2 minutes at 100°. Add 2 ml of water and neutralize the solution by addition of sodium hydroxide solution. Cool and filter the *p*-acetamino derivative; recrystallize from 2–3 ml methanol and add to the hot filtrate 0.5–1 ml of water. It may require two or three crystallizations to obtain a pure *p*-acetamino derivative melting at 105–106°. The yield is about 30–50 mg.

Note: When the diacetamino derivative is desired, the nitration mixture consists of 3 ml of concentrated sulfuric acid and 1.5 ml of concentrated or fuming nitric acid. All other directions are the same.

13.7 Picrate of naphthalene. Dissolve 100 mg of naphthalene in 6 ml of hot methanol; cool the solution and add 1.5 ml of a saturated solution of picric acid in methanol. Filter the solid with suction and wash with 0.5 ml of alcohol. Dry by pressing the crystals between filter paper and determine the melting point at once. The yield is 40–50 mg of crystals, melting at 148°.

Note: An alternative procedure is to use dry benzene as a solvent. Only a few hydrocarbons yield pure stable picrates. Even when benzene is used and the picrate is filtered immediately after mixing the reagents, results are only slightly better than when methanol or ethanol is used as a solvent.

13.8 Styrene dibromide. Dissolve 0.2 ml of styrene in 1 ml of dry carbon tetrachloride. Add 10 drops of bromine (use care in handling bromine) and then cool the tube. Add to the solid mass of crystals that separates out 5 ml of methanol, heat until the mixture dissolves, and then filter and cool the filtrate. The yield of the dibromide, melting at 71–2°, is about 300 mg.

13.9 Oxidation of cyclohexene to adipic acid. In a 125-ml Erlenmeyer flask add 1.5 g of potassium permanganate, 25 ml of water, and 1 ml of 6 *N* sodium hydroxide solution. Warm to effect solution of the permanganate; add 0.3 ml of cyclohexene and, after stoppering the flask with a solid rubber stopper, shake at intervals for 10–15 minutes or until the odor of cyclohexene has completely disappeared. Filter with suction and evaporate the filtrate to dryness; add 2 ml of 6 *N* hydrochloric acid solution and 3 ml of water. Extract three times with 5 ml of ether.

Evaporate the ether and crystallize the residue from hot water. The yield is 50–60 mg of adipic acid, melting at 149–151°.

13.10 Aroylbenzoic acids. Use apparatus shown on page 178. Place in the tube a mixture of 10 ml of carbon disulfide, 400 mg of phthalic anhydride, 800 mg of anhydrous aluminum chloride, and 400 mg of the hydrocarbon to be identified. Heat the mixture in a water bath until no more hydrogen chloride is evolved. Remove the test tube and cool in tap water. If the mixture separates into two layers, the upper carbon disulfide layer is decanted; if it does not, 10 ml of 6 *N* hydrochloric acid is added, drop by drop at first, and later in 1-ml portions with frequent stirring. The resulting product, if solid, is separated by filtration and washed with two 5-ml portions of cold water. If a viscous liquid separates, the mixture is cooled in an ice bath until it solidifies; the aqueous layer is decanted and the residue is washed in the test tube with two 5-ml portions of cold water. The product in either case is transferred to a small beaker and boiled for one minute with a mixture of 10 ml of 6 *N* ammonium hydroxide, 20 ml of water, and about 100 mg of decolorizing carbon. The solution is filtered by suction while hot, and the filtrate is poured into about 25 g of crushed ice contained in a small beaker, and then acidified with 6 *N* hydrochloric acid with stirring. After standing for ten minutes, the precipitate of aroylbenzoic acid is brought upon a filter, washed with small portions of water until free from acid, and dried in air. The product is recrystallized by dissolving in 3–4 ml of alcohol, filtering while hot, and then adding about 7 ml of water and cooling the filtrate.

Note: For *n-propylbenzene*, *n-butylbenzene*, *cumene*, and *cymene* the general procedure is modified as follows. Use 2.5 times the quantities of reagents except carbon disulfide, of which 10 ml is sufficient. At the end of the reaction, the tube is cooled and the carbon disulfide layer removed; then 15 ml of 6 *N* hydrochloric acid is added with the precautions previously mentioned. After cooling the mixture in an ice bath, the aqueous layer is decanted, and the oily product is washed with two 5-ml portions of cold water. To remove the unconverted hydrocarbon, a current of steam is passed through this mixture until the odor of the former is no longer perceptible. The aqueous layer is then decanted and the residue extracted under reflux with three 20-ml portions of ligroin (b. p. 90–120°). The combined ligroin extractions are cooled in an ice-bath, and the gummy precipitate of aroylbenzoic acid that appears is allowed to stand with occasional stirring until it becomes granular. The solid is collected on a filter, dried in air, and finally recrystallized.

For ethylbenzene and the three xylenes tetrachlorophthalic anhydride is used. It is more convenient, however, to derivatize the three xylenes by nitration and ethylbenzene through the *p*-acetamino derivative.

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Derivatives of Sulfur Compounds

Thioalcohols (mercaptans) and thiophenols. Suitable derivatives for the characterization of thioalcohols and thiophenols may be prepared by converting them into solid thioethers or thioesters as shown by the following equations:

$$RSH \xrightarrow{NaOH} RSNa + Cl\text{-}C_6H_3(NO_2)_2 \longrightarrow (NO_2)_2C_6H_3\text{-}S\text{-}R$$

2,4-Dinitrochlorobenzene → 2,4-Dinitrophenyl thioether

$$(O_2N)_2C_6H_3\text{-}S\text{-}R \xrightarrow{[KMnO_4]} (O_2N)_2C_6H_3\text{-}SO_2\text{-}R \quad (1)$$

2,4-Dinitrophenyl sulfone

$$(O_2N)_2C_6H_3\text{-}COCl + R\text{-}SH \xrightarrow{NaOH} (O_2N)_2C_6H_3\text{-}COSR + NaCl + H_2O \quad (2)$$

3,5-Dinitrobenzoyl thioester

$$NO_2C_6H_3(CO)_2O + RSH \longrightarrow NO_2C_6H_3(COSR)(COOH) \quad (3)$$

3-Nitrophthalic thioester

$$\alpha\text{-}C_{14}H_7O_2SO_3Na \xrightarrow{RSH} \alpha\text{-}C_{14}H_7O_2SR + NaHSO_3 \quad (4)$$

Sodium anthraquinone α-sulfonate → Anthraquinone α-alkyl thioether

Equation (1) represents the preparation of a *2,4-dinitrophenyl thioether* by reacting the mercaptan with 2,4-dinitrochlorobenzene. The reaction takes place with ease when a sodium mercaptide solution is added to an alcoholic solution of the aromatic nitrohalide. The thioether separates on cooling; for further identification the thioether may be oxidized to the corresponding sulfone. The preparation of these derivatives is convenient for the characterization of many mercaptans.

Equations (2) and (3) represent the formation of *thioesters* by reacting the mercaptan with 3,5-dinitrobenzoyl chloride or 3-nitrophthalic anhydride. The preparation of the 3,5-dinitrobenzoyl thioester should be a second choice for the beginner. The method for the preparation of the esters is similar to that used for the alcohols. About 200 mg of the acid chloride or the anhydride are heated with 5–6 drops of the thiol until a uniform melt has been obtained; a few drops of pyridine may be added in the reaction of the thiol with the acid chloride to aid the removal of hydrogen chloride. After addition of water, the solid derivative is filtered and purified by crystallization.

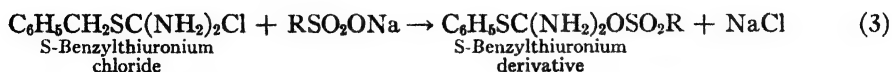
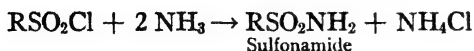
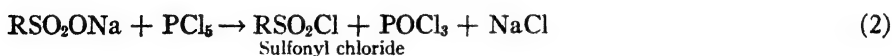
Equation (4) represents the preparation of a *solid thioether* by reacting the thiol with sodium anthraquinone α-sulfonate; the thioether may be oxidized to the corresponding sulfone; another anthraquinone derivative proposed for the same purpose is 1,5-butyl-anthraquinone-sulfone sodium sulfonate. One disadvantage of this method is that the reaction takes place slowly, requiring several hours of heating.

Sulfonic acids and sulfonyl chlorides. The characterization of sulfonic acids is almost entirely based on the preparation of derivatives, since they do not have well-defined boiling points and melting points. A variety of derivatives have been proposed in the literature, and the most important are illustrated by the following equations:

$$\underset{\text{Sodium sulfonate}}{RSO_2ONa} + \underset{\text{Arylamine salt}}{[Ar\overset{+}{N}H_2H]\overset{-}{Cl}} \rightarrow \underset{\text{Arylamine sulfonate}}{[Ar\overset{+}{N}H_2H]\overset{-}{O}SO_2R} + NaCl \qquad (1)$$

$$RSO_2ONa + PCl_5 \rightarrow \underset{\text{Sulfonyl chloride}}{RSO_2Cl} + POCl_3 + NaCl \qquad (2)$$

$$RSO_2Cl + 2\,NH_3 \rightarrow \underset{\text{Sulfonamide}}{RSO_2NH_2} + NH_4Cl$$

$$\underset{\text{S-Benzylthiuronium chloride}}{C_6H_5CH_2SC(NH_2)_2Cl} + RSO_2ONa \rightarrow \underset{\text{S-Benzylthiuronium derivative}}{C_6H_5SC(NH_2)_2OSO_2R} + NaCl \qquad (3)$$

Equation (1) represents the formation of an *arylamine salt* of the sulfonic acid; the amines that have been proposed in the literature for the identification of sulfonic acids are aniline, *o*-toluidine, *p*-toluidine, pyridine, *p*-nitrobenzylpyridine, and phenylhydrazine. The first three

arylamines are recommended for beginners. The salts are easily prepared by heating together an aqueous solution of the free acid or of the alkali salt, a slight excess of the amine, hydrochloric acid, and enough water to bring all of the material in solution at the boiling point. The salt separates out on cooling, and, after filtration, it is recrystallized from 1 per cent acetic acid to minimize hydrolysis. Aromatic aminosulfonic acids must first be acetylated in order to form the arylamine salt. An alternative method is to remove the amino group; the amino sulfonic acid is diazotized, and the diazo group is replaced by chlorine through the Sandmeyer reaction. The method may be applied to about one gram of material.

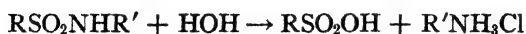
Equation (2) represents the method most commonly employed and is recommended as third choice for beginners; it involves the conversion of the *alkali sulfonate* to the *sulfonyl chloride* by treatment with phosphorus pentachloride. The sulfonyl chloride is ammonolysed to the *sulfonamide* or converted to the *anilide*. The disadvantage of this method is that it requires 1–2 g of the dry salt and considerable more time and work than the other methods; in addition, the method is not applicable to compounds containing groups that react with phosphorus halides.

Equation (3) represents the formation of the *S-benzylthiuronium* derivative. A number of sulfonic acid derivatives suitable for characterization work are prepared by reacting the alkali sulfonate with *S*-benzylthiuronium chloride. The reagent is easily prepared by refluxing an alcoholic solution of benzyl chloride and thiourea. A concentrated neutral solution of the sodium or potassium salt of the sulfonic acid to be derivatized is added with stirring to a slight excess of the reagent dissolved in water; the method is satisfactory for mono- and disulfonic acids if other functional groups are absent. The presence of hydroxy or amino groups is disadvantageous.

A number of important naphthalene substituted sulfonic acids may be identified in micro quantities by microscopic examination of the *benzoyl* or *S-benzythiuronium* derivatives.

Sulfonamides. Hydrolysis of the sulfonamide will yield a sulfonic acid and ammonia or an amine:

$$RSO_2NH_2 + HOH \rightarrow RSO_2OH + NH_4Cl$$

$$RSO_2NHR' + HOH \rightarrow RSO_2OH + R'NH_3Cl$$

The hydrolysis is effected by heating with 25 per cent hydrochloric acid, 80 per cent sulfuric acid, or a mixture of 85 per cent phosphoric acid and 80 per cent sulfuric. In the case of a substituted sulfonamide, the amine may be separated by making the solution alkaline and distilling if the

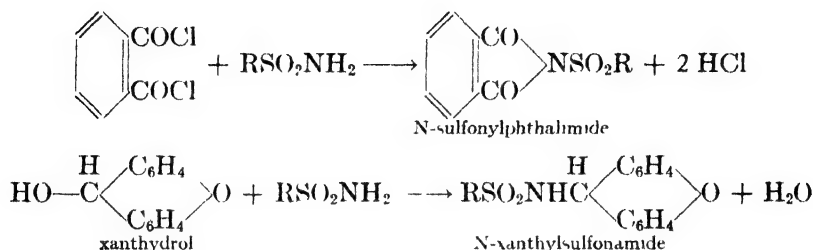
amine is volatile, or extracting with an appropriate solvent; thus it is possible to identify both the amine and the sulfonic acid.

Unsubstituted sulfonamides, RSO_2NH_2, may be reacted either with phthalyl chloride to give *N-sulfonylphthalimides* or with xanthydrol to form *N-xanthylsulfonamides.*

$$C_6H_4(COCl)_2 + RSO_2NH_2 \longrightarrow C_6H_4(CO)_2NSO_2R + 2\ HCl$$

N-sulfonylphthalimide

$$HO\text{—}CH(C_6H_4)_2O + RSO_2NH_2 \longrightarrow RSO_2NHCH(C_6H_4)_2O + H_2O$$

xanthydrol N-xanthylsulfonamide

The preparation of N-xanthylsulfonamides may be applied successfully, using semimicro quantities; however, only about a dozen derivatives have been reported, and the method is not successful in benzenoid amides which contain branched alkyl groups on the ring. The alkylation of sulfonamides that have amino hydrogen has been used to prepare derivatives. Either alkyl halides, such as methyl iodide and ethyl bromide, or alkyl sulfates may be used for the alkylation.

13.11 Preparation of 2,4-dinitrophenyl thioethers from thiols. Place in an 8-inch tube 8 ml of methanol, 3 millimoles of the mercaptan, and 3 millimoles of sodium hydroxide (9–10 drops of 6 *N* sodium hydroxide solution). Add the sodium mercaptide solution to a tube containing 600 mg of 2,4-dinitrochlorobenzene dissolved in 4 ml of methanol. Add a boiling stone and arrange for reflux. Boil the mixture gently for 5–10 minutes and filter the solution rapidly while hot. Cool for 10 minutes and filter the solid thioether. Recrystallize once or twice from methanol.

Note: If a red coloration results when the sodium hydroxide solution is added to the alcoholic solution of the mercaptan, a slight excess of the latter is used in order to remove the color caused by excess of alkali.

For further identification of the thioether, it may be converted by oxidation to a sulfone, as outlined in Procedure 13.12.

13.12 Oxidation of 2,4-dinitrophenyl thioethers to sulfones. Dissolve 3 millimoles of the thioether in the minimum quantity of glacial acetic acid and treat it with 0.7 g of potassium permanganate dissolved in 25 ml of water. Add the permanganate solution in portions of 2–3 ml, shaking after each addition until the color is discharged. Continue the addition of permanganate until the color persists after shaking for several minutes. Remove the excess of permanganate by careful addition of sodium bisulfite solution; the sulfone precipitates at this point on

cooling by addition of 25–30 g of ice. Filter the solid and dry by pressing the solid between filter paper. Purify the sulfone by crystallization from methanol.

13.13 Preparation of 3,5-dinitrothiobenzoates from thiols. Dry an 8-inch tube by heating it over a flame and then stopper it with a cork and allow to cool. Place 200 mg of 3,5-dinitrobenzoyl chloride and arrange for reflux. Add to the solid chloride 5–6 drops of the thiol and 1 drop of pyridine. Adjust the microburner so that the reaction mixture melts into a homogeneous mass and heat in this manner for about 10 minutes. If at this point a strong odor of the thiol persists, add 25–50 mg of the chloride and heat for an additional 5 minutes. Add 2 ml of water, cool, and stir by means of a glass rod until the oily mass solidifies. Filter with suction and wash with water. To remove the small amount of 3,5-dinitrobenzoic acid and to crystallize the derivative, follow the directions given in Procedure 10.2, page 222.

13.14 Preparation of arylamine salts of sulfonic acids. The following directions apply to the preparation of the sulfonates of aniline, *o*-toluidine, and *p*-toluidine.

Dissolve about 200 mg of the sodium salt of the sulfonic acid in water, using an 8-inch tube; if the free sulfonic acid is available, use the same amount and dissolve it in the minimum amount of water or dilute sodium hydroxide. For the barium salt of the sulfonic acid, use 300 mg and boil it with 2 ml of water and 1 ml of 6 N sulfuric acid; add a minute amount of charcoal or filter-cell and filter the hot solution to remove the barium sulfate.

To the solution of the alkali sulfonate or free sulfonic acid, add 300 mg of the arylamine (aniline, *o*-toluidine, or *p*-toluidine), 1–2 ml of 6 N hydrochloric acid, and enough water to bring all the material in solution at the boiling point. Add about 50–100 mg of charcoal, filter the hot solution, and cool. Filter the arylamine sulfonate and recrystallize to constant melting point from 1 per cent acetic acid.

Note: The arylamine salt should be thoroughly dried before the melting point is determined. When the salt melts above 180°, the sample may be dried by pressing the material on a filter paper, but the capillary should be placed in the bath when the temperature is below 100° to insure proper drying while the temperature of the bath rises.

In selecting the arylamine it is suggested to the beginner to use either aniline or *p*-toluidine, since these are commonly available in the laboratory in a greater state of purity than *o*-toluidine.

13.15 Preparation of sulfonyl chlorides from sulfonic acids and their salts. Arrange a distilling tube as shown on page 178, but omit the re-

flux condenser. Place in the tube 1 g of finely pulverized phosphorus pentachloride; the material is rapidly pulverized in a hood, using a mortar and pestle, and transferring it immediately into the distilling tube. Add to the phosphorus halide 500 mg of dry and finely pulverized acid or its alkali salt. Raise an oil bath under the distilling tube and heat to 100–108° for about 30 minutes; then raise the temperature to 140° in order to distil over the phorphorus oxychloride. For this purpose the receiving tube containing the water is raised so that the water level is just below the outlet of the side arm. The oil bath may be omitted if a good micro-burner with an adjustable flame is available. In such a case a thermometer is inserted through the rubber stopper so that it reaches the bottom of the distilling tube. The flame may be adjusted so that the initial and final heating is done at the temperatures indicated. The tube is cooled, and 2–3 ml of ice water are added; the mixture is stirred by means of a glass rod to wash the sulfonyl chloride and remove the phosphorus halides. Decant the aqueous layer, being careful that the oily sulfonyl chloride adheres to the sides of the tube and stirring rod. Repeat the washing with ice water and decant the washings. The crude product is ammonolyzed to the sulfonamide as directed in Procedure 13.16 below.

If a pure sample of the sulfonyl chloride is desired, then it is recommended to start with 1–2 g of the sulfonic acid and double its weight of phosphorus pentachloride. The procedure is the same as described until the removal of phosphorus oxychloride. About 10 ml of benzene are then added, and the mixture is transferred into a separatory funnel; the distilling tube is washed with 5 ml of the organic solvent, and the washings are united with the main portion of the solution. The benzene solution is washed twice with 10 ml of ice water and then transferred into a small flask and dried with anhydrous calcium chloride. The dry benzene solution is transferred into a distilling tube, and the solvent is removed by distillation until the volume of the solution is about 4–5 ml. At this point it may be transferred to a small distilling tube arranged for vacuum distillation, and the crude sulfonyl chloride is distilled at a pressure of 10–20 mm.

If the sulfonyl chloride can be crystallized from carbon tetrachloride, chloroform, or petroleum ether, the vacuum distillation may be omitted, and the crude product purified by crystallization. In such a case the benzene is entirely removed and 3–4 ml of the solvent added and heated to boiling. If any appreciable amount of oil remains undissolved at the sides of or at the bottom of the distilling tube, the amount of solvent is cautiously increased until complete solution is effected at or near the boiling point of the solvent. The hot solution is filtered and cooled in an

ice-salt mixture. The solid mass that separates out is filtered rapidly, washed with a small amount of the pure solvent, and dried in a vacuum desiccator.

13.16 Ammonolysis of sulfonyl chlorides to sulfonamides. Use the crude sulfonyl chloride prepared in Procedure 13.15 above from 500 mg of the sulfonic acid or its salt. Add to the distilling tube containing the crude sulfonyl chloride 10 ml of concentrated solution of aqueous ammonia and 2 g of powdered ammonium carbonate. Stir the mixture for a few minutes by means of the stirring rod that was used in washing the chloride and set aside for 5 minutes. Warm at 60° for 15 minutes, then to 80–90° for 10 minutes, and cool. Filter any solid that separates out at this point and evaporate the filtrate to dryness on the water bath. The residue of crude sulfonamide is crystallized separately from any amount that separated from the initial solution. For crystallization the sulfonamide is dissolved in 10–25 ml of boiling water; the solution is treated with charcoal, filtered, and cooled.

13.17 Preparation of S-benzylthiuronium derivatives of sulfonic acid. Prepare the reagent if it is not available in the laboratory by heating for 20–30 minutes under reflux 2 g of benzyl chloride, 1.2 g of thiourea, and 3 ml of methanol. Cool the pale-yellow solution in an ice-water mixture and filter the mass of crystals by suction. Wash twice with 1-ml portions of ethyl acetate. Dry the product rapidly by pressing between filter papers and place in a stoppered tube. The yield is 2.5–3.0 g.

Dissolve 200 mg of the sodium or potassium salt of the sulfonic acid in the minimum amount of water; in the case of the free sulfonic acid, dissolve 200 mg in dilute sodium hydroxide solution (0.5 ml of 10 per cent sodium hydroxide solution and 1 ml or more of water). Add a drop of phenolphthalein and neutralize the excess sodium hydroxide by addition of dilute hydrochloric acid solution. Prepare separately in a test tube a water solution of 250 mg of S-benzylthiuronium chloride for each acidic group present in the sulfonic acid molecule. For example, use 250 mg of the reagent if the acid taken is 1-naphthalene sulfonic acid (200 mg), but use 500 mg of the reagent if the acid (200 mg) taken is naphthalene-2,7-disulfonic acid. Cool both solutions and mix by adding the sulfonic salt solution to the reagent slowly with shaking. If this procedure fails to give the derivative, dissolve the benzylthiuronium chloride in sufficient hot alcohol to give a 15 per cent solution and add to this the sulfonic acid salt solution. The derivative is filtered, washed with water, and recrystallized by dissolving in the minimum amount of hot alcohol; to the filtered solution add water dropwise until a permanent cloudiness results. Dry the crystals rapidly by pressing between filter paper or by

placing in a vacuum desiccator. The derivatives often develop an offensive odor, due to the formation of benzylthiol (benzylmercaptan) by decomposition of the thiuronium chloride.

13.18 Hydrolysis of sulfonamides. Place in a distilling tube 1 ml of concentrated sulfuric acid (sp. g. 1.84) and add cautiously 5 drops of water and 1 ml of 85 per cent phosphoric acid in the order given. Add 500–800 mg of the sulfonamide, place a thermometer into the tube, and heat gradually until the temperature reaches 160°. Keep the temperature at 155–165° for about 5–10 minutes or until the sulfonamide has passed into solution. Cool the dark viscous solution and add to it 6 ml of water. Add slowly 25–30 per cent sodium hydroxide solution while the mixture is cooled until it is distinctly alkaline.

If the amine resulting from the hydrolysis of the sulfonamide is volatile, the tube is arranged for distillation, and, after addition of boiling stones, the alkaline mixture is distilled until the volume is reduced to one half; after 8 ml of distillate have been collected, a drop is collected separately and tested with litmus or *p*H paper; if it is alkaline, the distillation is continued; otherwise it is discontinued. The distillate may be used directly for benzoylation as described in Procedure 11.15 (page 258), or, if the free amine is desired, it may be extracted with ether; the extract, after drying with a few pellets of sodium hydroxide, is distilled to remove the solvent.

If the amine resulting from the hydrolysis of the sulfonamide has a low volatility, it may be extracted with ether directly from the cold alkaline solution. The ether extract is contaminated with hydrolytic decomposition products; therefore, after the evaporation of ether, the tarry mass is boiled with 3 ml of water, 1 ml of 6 *N* hydrochloric acid solution, and a pinch of charcoal and filtered. The filtrate is made alkaline, and the amine is extracted or derivatized. The residue remaining in the distilling tube is poured into an evaporating dish, treated with 100 mg of charcoal, evaporated to about 4–5 ml, and filtered while hot. The solution is carefully neutralized and then used for the preparation of the arylamine salt or benzylthiuronium derivative.

13.19 Preparation of N-xanthylsulfonamides. Place into an 8-inch tube provided with a clean solid rubber stopper 10 ml of glacial acetic acid, 200 mg of xanthydrol, and 200 mg of the sulfonamide. Shake the mixture for 2–3 minutes. Filter the solid and crystallize from dioxane-water (3:1). One crystallization is usually sufficient.

Note: The following 12 sulfonamides have been derivatized, using xanthydrol as a reagent; the number following the abbreviation of the sulfonamide is the melting point (uncorrected); Benzenesulfonamide-1: 2-Me-, 200; 4-Me-,

183; 4-Et-, 196; 4-n-Pr-, 200; 4-n-Bu-, 186; 4-n-Am-, 165; 3,4-di-Me-, 190; 2,4-di-Me-, 188; 2,5-di-Me-, 176; 2,4,6-tri-Me-, 204; 4-NH_2-, 208; Saccharin-, 199.

Selected References on Sulfur Compounds

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SULFONAMIDES

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Alkylated p-toluenesulfonamides. Carothers, Bickford, and Hurwitz, *J. Am. Chem. Soc.*, **49**, 2913 (1927).

Derivatives of Miscellaneous and Physiologically Active Compounds (Drugs, Vitamins, Hormones, and Heterocyclic Bases)

Table 42 lists about 250 compounds that may be classified as follows:

(1) Important synthetic organic compounds used in medicine as ***drugs:*** antipyrine, pyramidone, chlorobutanol, novocain, phenobarbital, sulfathiazole, and the like.

(2) Compounds designated as *vitamins*, *hormones*, and *auxins*.

(3) The most important nitrogenous compounds derived from plants and designated as *alkaloids:* morphine, hyoscyamine, atropine, quinine, papaverine, strychnine, and the like.

(4) Miscellaneous compounds derived from or related to animal or plant metabolic processes. For example, in Table 42 are listed such compounds as cholesterol, cholic acid, indole, skatole, hydantoin, xanthine, urea, uric acid. A few of these have appeared in other tables. For example, urea is listed in Table 22 under the amides. It was included in this table, however, because it has been possible to include specific reactions for identification, and literature references that could not be listed under the general treatment of the other table.

(5) Miscellaneous compounds that are either important reagents (nitron, xanthydrol, cupferron, flavianic acid) or are used extensively in industry as for example triphenyl phosphate, trioxymethylene, tetramethylthiuram disulfide ("Thiuram," "Vulcacit"), abietic acid, melamine and the like.

The compounds in Table 42 are arranged according to increasing melting point. The notes that follow (in abbreviated form) give: (a) the derivatives that may be used for their identification; (b) chemical reactions useful in their characterization; (c) color reactions and other tests useful in their identification; (d) literature references. A list of the abbreviations used in Table 42 will be found on pages 355–357.

CHAPTER 14

Separation of Mixtures

THE reader is familiar with the problem of separating mixtures in connection with the purification of the major product of typical organic preparations. In such cases the attention is focussed on merely getting rid of the by-products of the reaction, and only the one desired product is recovered. Furthermore, it is generally possible to determine the chemical nature of the components that are to be separated from the reagents used and from the conditions of the reaction. A systematic procedure may be worked out to separate such known mixtures by taking advantage of the known differences in the chemical and physical properties of the components.

A mixture of unknown composition presents a much more difficult problem, for there is no one scheme that can be used for the separation of all kinds of organic mixtures. The objective is to separate the mixture into pure components. Each component may then be identified.

Broadly speaking, most of the effective methods depend on differences either in solubility or in volatility. Sometimes these differences exist among the original components of the mixture; sometimes they must be created by chemical reactions. The relationships of chemical structure to solubility have been briefly discussed in Chapter 4. Volatility seems to depend much more on the molecular structure than on molecular weight. The greater the polar characteristics of a molecule, or the greater the tendency of the molecule to associate with other molecules, such as in hydrogen-bonding, the less volatile that compound will be in comparison with other molecules of similar molecular weight. Alcohols, which are slightly polar compounds and also tend to associate, have much higher boiling points than ethers of the same molecular weights. *o*-Nitrophenol is chelated and therefore nonpolar. It is capable of being steam-distilled, whereas the isomeric nitrophenols, which are polar, cannot be steam-distilled.

The more important methods for separating mixtures are:

1. Fractional distillation.
   a. Direct distillation at atmospheric pressure.
   b. Distillation under reduced pressure.
   c. Steam-distillation.

2. Extraction by solvents without chemical change.
3. Extraction by solvents that produce chemical change.
4. Fractional crystallization.
5. Chromatographic techniques (Chapter 15).
6. Various combinations of the above five methods.

With binary mixtures separation is much easier to achieve than with mixtures of greater complexity. Binary mixtures of appropriate compounds should be separated by each of the above methods so as to acquire skill in the procedures. In addition, it is good training to separate unknowns that have been specifically prepared for each method. Chapter 2 should be reviewed for detailed suggestions regarding apparatus and techniques.

Preliminary tests for a general mixture. If nothing is known about the probable composition of a mixture under examination, a series of preliminary tests will be necessary before the most likely procedure for its separation can be determined. All of the results of these tests should be thoroughly considered before a scheme of separation is prepared. The scheme should be inclusive enough to cover all of the possibilities. The experienced worker will be able to take short-cuts intelligently, but the best policy for a beginner to follow is to assume that all types of compounds are present unless he can establish their absence by the preliminary tests. As the separation of the mixture progresses, these preliminary tests should be repeated on each fraction. It will frequently be found advantageous to run selected functional-group tests from Chapter 6 on the various fractions, or even on the original mixture.

If the mixture consists of more than one liquid phase, or of a solid phase in a liquid, these phases should be separated, and treated individually. In such mixtures, it is probable that the same compounds will exist in more than one of the phases. It is important that the preliminary tests be run on representative samples of the mixture, so that all the components will be tested. A complete record should be kept of all the tests made, including the results of the tests and the deductions that are made. It is wise, also, to keep a record of classes that are eliminated as possibilities because of the results of the tests. All samples that are to be set aside for later examination or use should be adequately labeled.

The following tests should be made, together with any others that the nature or behavior of the mixture may suggest:

1. Composition. The tests suggested in Chapter 3 are recommended. Care should be taken, in making the analysis for the elements, to insure

that all components of the mixture are present in the sample taken for the fusion with sodium (test for water; dehydrate before fusing with sodium). In the preparation of the scheme for separating the mixture, it is extremely important to know what elements are present.

2. *Solubility.* Solubility determinations should be made on well-mixed samples, utilizing all of the solubility classification solvents, as discussed in Chapter 4. It should be recalled that one or more of the components of the mixture may dissolve in any one solvent, and also that the same compound may partially dissolve in more than one solvent. The solubility in ether should be determined even if the material is not soluble in water. Other solvents that may be used to advantage include: methanol, ethanol, carbon tetrachloride, and chloroform. In cases where it is difficult to determine whether or not the solvent has dissolved appreciable amounts of the mixture, the solvent should be separated from the residue and distilled. Exceptions to this technique would be solutions in sodium hydroxide or sulfuric acid. An alkaline extract should be tested by acidifying it and extracting with ether. In the case of concentrated sulfuric acid as a solvent, some classes of compounds that dissolve in it may be recovered by pouring the acid onto an excess of cracked ice.

In evaluating the data from the solubility tests, it is essential not to lose sight of the elements that were found present in the mixture.

3. *Distillation.* Where a liquid mixture is involved, a 5-ml portion is carefully distilled. The boiling range is noted and particular attention is given to the distillation over this range to ascertain whether or not fractional distillation is practical. It is unwise to place too great reliance on the boiling range as regards the presence of specific compounds, since many of the common organic compounds form azeotropic boiling mixtures. This is the reason why fractional distillation cannot be used for some mixtures.

Any evidence of thermal decomposition of any of the compounds during the distillation should be noted and, if decomposition is evident, the distillation should be abandoned. In other cases, it should be observed whether a solid residue remains after distillation is complete; if such a residue exists, it should be steam-distilled. The various fractions obtained by distillation should be examined. Distillation under reduced pressure should be considered if normal distillation is unsatisfactory.

4. *Solid mixtures.* In the case of solid mixtures that did not appear to be separable by cold solvents, hot solvents should be used in an attempt to separate the mixture by fractional crystallization. Steam distillation may often be used to advantage on solids.

5. Chemical tests. Selected tests from Chapters 5 and 6 should be applied to the original mixture, or to fractions that have been separated from it by the preliminary testing methods. Every ascertainable fact about the presence or absence of the various chemical classes in the mixture will aid in devising a scheme of separation that will have maximum effectiveness with the minimum number of operations.

A general procedure for the separation of mixtures. The following general scheme may be applied to the separation of a mixture into several fractions, many of which correspond to the usual solubility classes of Chapter 4. The scheme is offered with the belief that it will be a useful guide, and not with the opinion that it is a perfect answer to the problem. This scheme should be modified in accordance with the observed facts for any one mixture. The next section of this chapter takes up the problems of separating mixtures that are present within single fractions as separated by this scheme.

Beginners should make up and separate by this scheme a mixture of known composition containing about 2–3 g each of 4–5 compounds. Select compounds that will separate in different fractions. The time consumed in separating such a *known* will be more than repaid in the time saved in handling *unknowns* later.

The procedures outlined in the following eight steps are summarized in the flow-sheet on page 336. *The Roman numerals in the flow-sheet refer to the numbers of the Steps in which that procedure is described.*

If the mixture is a solid, or if the preliminary distillation test showed that there was no distillate below 100°C., Step I should be omitted. If the preliminary distillation showed the presence of a low-boiling amine, the distillate in Step I should be absorbed in 3 *N* HCl.

Step I. Place 10–15 ml of the liquid mixture in a 25 ml distilling flask or distilling tube. Using a well-cooled receiver, distil the mixture to remove all the components that distil below 100°C. The distillate may contain low-molecular weight members of practically all the non-aromatic classes of compounds. Generally speaking, the molecules will contain 5 or less carbon atoms. A few saturated cyclic hydrocarbons, a few heterocyclic compounds, and benzene also boil below 100°C. Most of these volatile compounds are soluble in both water and ether but the hydrocarbons and their halogen derivatives are not soluble in water. By noting the boiling range of the distillate, a good estimate may be made as to whether or not the distillate is a mixture. If the distillate is a mixture, chemical separation and solvent extraction will be possible in a few cases but resort will have to be made to very careful fractional distillation

for most of these mixtures. Test the distillate for the elements and make appropriate classification tests.

It should be noted that chemical reactions may occur between components of the original mixture during this period of heating, even if the compounds did not react in the cold mixture. For example, if a mixture of aniline hydrochloride, sodium benzoate, and ethanol is heated to distil the ethanol, ethyl benzoate is formed in good yield. Examination of a sample of the original mixture in comparison with the final results of the analysis will usually detect any such change in composition of the mixture during its separation.

Test the residue from the distillation for water. If it is present, it must be removed before proceeding to the next step.

Step II. The residue from Step I should be shaken with ether, using 5 ml of ether for each gram of the mixture. Allow the ether to remain in contact with the mixture for 3 minutes (shake occasionally). Treat any undissolved residue by Step III and save the ether solution for Step V.

Step III. Warm the ether-insoluble residue to drive off the ether. Add 5 ml of water for each gram of residue and shake the mixture vigorously. Remove the aqueous solution. Again extract the residue with water, using 10 ml of water for each gram of residue. The water will remove Solubility Division **W** compounds (see page 110). The two aqueous solutions may be combined, or they may be examined separately. Owing to marked differences in solubility among various components in this group, it is entirely possible that the two aqueous solutions represent a fair separation of Division **W** compounds. Examine the aqueous solution by evaporating the water out of a 5-ml sample. If the residue is extremely small, the Division **W** compounds are not represented in the mixture. If a residue exists after evaporating the water, test other samples of the aqueous solution for acidity, for carbohydrates, and for other likely types of compounds of the Division.

If carbohydrates are present, the water may be removed by vacuum distillation or by azeotropic distillation. The compound or compounds introduced for such purpose should be soluble in ether so that any of these liquids remaining after all the water has been distilled may be removed by ether extraction. Water-insoluble acids that are present in the original mixture as their soluble salts may be separated from the aqueous solution by making the solutions acidic with mineral acids and then distilling or extracting with ether. The salts of amines may be decomposed by sodium hydroxide and the amines removed by distillation or ether extraction.

Step IV. The ether-insoluble, water-insoluble residue from Step III

should be shaken with a volume of cool methanol equal to 5 times the weight of the residue. The alcoholic solution may be separated from any insoluble residue by filtration or decantation. The alcohol should then be distilled. Thus, an alcohol-soluble and an alcohol-insoluble fraction are obtainable. Examine these fractions for homogeneity. If either of the fractions appear to be mixtures, extract such a mixture with 10 per cent hydrochloric acid and with 10 per cent sodium hydroxide in an attempt to separate them further. If these extractions fail, fractional crystallization from various solvents should be tried.

Unfortunately, exact and complete data are lacking on the solubilities of most organic compounds in various solvents, including the common solvents. The attempt to use solvents in the separation of mixtures is further complicated by the fact that in many cases isomers of the same compound do not have similar solubilities. However, incomplete lists of some of the types of compounds that may be expected in the two fractions resulting from the methanol extraction are given below.

Some compounds insoluble in alcohol, ether, and water:

Many dinitro derivatives of the aromatic hydrocarbons and their amino, hydroxy, and acid derivatives.
Many trinitro compounds of the above types.
Several dihalo derivatives of anthracene.
Several amino-substituted sulfonic acids; a few amides and imides.
Benzyl and benzoyl ureas; several derivatives of anthraquinone.

Some compounds soluble in alcohol, but insoluble in ether and in water:

Some dibromo- and dinitro- benzoic acids and a few other aromatic acids.
Several polyhydroxy- and polyamino- quinones and quinolines.
A few aminophenols; a few amides and anilides; a very few amines.

Step V. Pour the ether solution from Step II into a distilling flask or distilling tube the capacity of which is twice the volume of the ether and distil the ether into a dry receiver. Save the ether for use in the next extraction. Cool the residue and then extract it twice with water, using 3 ml of water per gram of residue for the first extraction and 7 ml of water per gram of residue for the second extraction. These aqueous solutions will contain the Solubility Division **E** compounds (see page 110). Examine these two aqueous solutions separately, since many compounds of Division **E** are highly soluble in water, whereas others are only moderately soluble.

Since many compounds that are slightly soluble in water do not belong to Division **E**, the aqueous extract may be given some color or odor by such compounds. Extract the aqueous component with 5 ml of ether and discard the ether. To determine whether or not the water has re-

moved a Division **E** fraction, test the solution with litmus. Also distil a 5-ml portion, noting the boiling range, the properties of the distillate, and the residue. If it is concluded that one or more components have been removed by the water, saturate the aqueous solution with potassium carbonate. Any acids originally present will be converted to salts and most of the other compounds will separate from the salt solution. Shake the solution with half its volume of ether. Separate the ether layer and distil the ether. The residue will be the Division **E** compounds, with the exception of the acids. When acids have been detected in the aqueous extract by the litmus test, the potassium carbonate solution should be neutralized with dilute sulfuric acid to the yellow end-point of *Bromothymol Blue*, and the solution extracted with half its volume of ether. It is best to remove drops of the solution and add them to *Bromothymol Blue* test-paper, rather than add the indicator to the solution. The ether extraction will remove most of the phenols or amides that were present in the aqueous solution. The aqueous solution should now be made definitely acidic with dilute sulfuric acid and distilled to remove the volatile acids. If some acid is precipitated in the water when it is acidified, it may be removed by ether extraction.

Step VI. The residue that was insoluble in water at the beginning of Step V should be dissolved in ether. (If nitrogen was absent in the residue, omit the remainder of this step and proceed to the next one.) Place the ether solution in a separatory funnel and shake it thoroughly with one-fourth its volume of 10 per cent hydrochloric acid. Separate the two layers. Again extract the ether with one half its volume of 10 per cent hydrochloric acid. The acid will remove Solubility Division **H** compounds. The two acidic solutions should be examined separately on the chance that some separation of the amine components may have been accomplished. Make the solutions slightly alkaline with 10 per cent sodium hydroxide. Extract them twice with ether and combine the ether solutions. Dry the ether solution with anhydrous sodium carbonate and distil the ether to obtain the Division **H** fraction.

It should be recalled that many amines are not extractable by dilute acids and will be found in the Division **M** fraction.

Step VII. Shake the ether solution remaining after the Division **H** compounds have been removed in Step VI with half its volume of 10 per cent sodium hydroxide solution. Extract the ether again with half as much 10 per cent sodium hydroxide solution. Combine the two alkaline extracts and warm the mixture to drive off the dissolved ether. Neutralize the alkaline solution to the yellow end-point of *Bromothymol Blue* by adding dilute hydrochloric acid dropwise, while vigorously stirring the

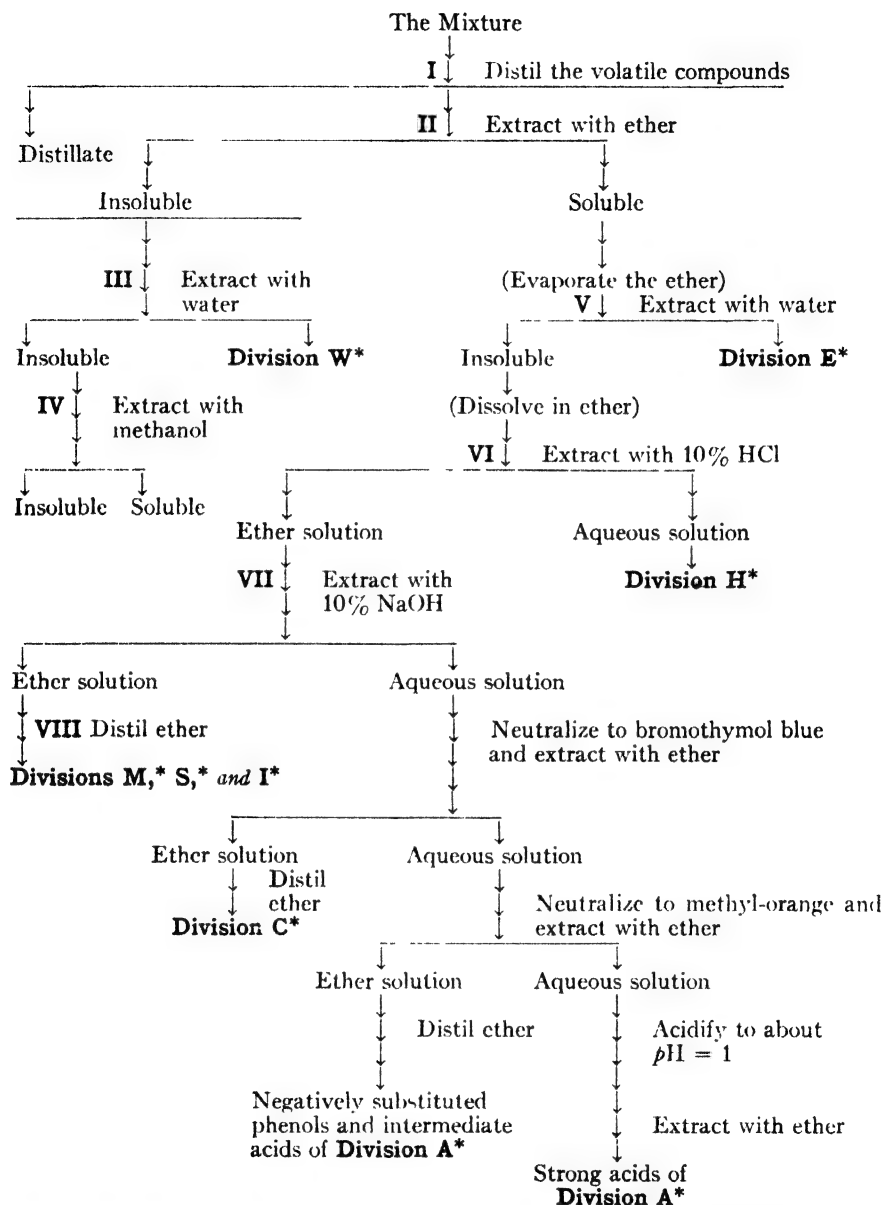
solution. To test the solution for the proper *p*H, remove a drop of the mixture from time to time and apply it to a strip of *Bromothymol Blue* test-paper. If the indicator is added directly to the solution, it will be extracted by ether and cause confusing colorations. Now extract the aqueous solution twice with ether to remove the Solubility Division **C** compounds. Dry the ether with anhydrous sodium sulfate. Decant the ether and distil it, leaving the Division **C** compounds as the residue. Not all the phenols will be extracted at the *p*H used and the later acid fraction should be tested for phenols.

The aqueous solution from which most of the phenols and other weakly acidic compounds have been extracted should be further acidified to the end-point of *Methyl Orange.* Ether extraction at this *p*H will remove most of the negatively substituted phenols and the intermediate acids. This fraction represents the less acidic members of Division **A** compounds.

Concentrate the aqueous solution by evaporation to about half its original volume. Cool the solution and acidify it to the red end-point of *Thymol Blue.* Extract the solution with ether to get out the most acidic compounds of Division **A**.

Step VIII. The ether solution from which the acids have been removed should be washed twice with 5-ml portions of water to remove any remaining sodium hydroxide. Dry the ether with an anhydrous salt and decant and distil it. The residue will contain compounds that are in Solubility Divisions **M**, **S**, and **I**. Suggestions for further separation of this mixture are given on pages 338–339.

Suggestions for separating intraclass mixtures. Assuming that the mixture was treated by the scheme suggested, it has been separated into a maximum of ten fractions. It is improbable, however, that any one mixture will contain compounds that would separate in all ten of these fractions. Because of overlapping solubilities, it is entirely possible that some of the compounds have been partially separated in two or more fractions. This fact should be kept in mind when the individual fractions are purified, and tests are being performed on them.

In connection with attempts at purification of the individual fractions, it may be discovered that the fraction represents a mixture of two or more compounds, not counting the impurities due to imperfect separation. No simple set of directions can be given for the separation of such intraclass mixtures. The usual methods of distillation, fractional extraction, and fractional precipitation are often useful. Hot solvents, the less commonly used solvents, and mixed solvents should also be tried. Occasionally, resort may have to be made to chemical reactions that will

*** Refer to the Divisional Solubility Classifications for the classes and subclasses of compounds that may be present (pages 110–111).**

make separation possible. Benzene may be separated from cyclohexane by nitrating or sulfonating the benzene (see Procedure 8.1, page 159). A mixture of an ester and an ether that cannot be fractionated may be separated by saponifying the ester (Procedures 10.12 and 10.13, page 232).

Mixtures of Division **W** *compounds.* Aqueous mixtures of Division **W** compounds should be tested for carbohydrates, amine salts, metallic salts, and ammonium salts. If carbohydrates are absent, such mixtures may be distilled to remove the water but, if carbohydrates are present, it is best to distil under reduced pressure. If amine salts are present, make the mixture alkaline and then steam-distil. The salts of acids could, of course, be converted to free acids by adding a mineral acid. The acids thus liberated may or may not be extractable by ether, or be capable of being steam-distilled. In general, molecules having two or more polar groups cannot be steam-distilled.

Hot alcohol is a convenient solvent for separating mixtures of Division **W** compounds after the water has been removed from the mixture. Sugars do not dissolve in the hot alcohol. Most of the carboxylic acids will dissolve in hot alcohol but will crystallize out on cooling. Many of the other compounds of this class remain in solution in the alcohol and may be recovered by distilling the alcohol.

The hydrogen atom in chloroform is an *acceptor* in hydrogen-bonding. Hence, compounds having functional groups that act as *donors* will dissolve in chloroform, even if they do not dissolve in carbon tetrachloride. Chloroform will extract some types of compounds from nonaqueous mixtures of this class.

Mixtures of Division **E** *compounds.* If the aqueous mixture of Division **E** compounds is either acidic or basic, neutralize the solution. Steam distillation will separate the volatile components from the salts, the polyhydroxy phenols, and other nonvolatile compounds. The nonvolatile residue may often be separated by fractional crystallization from hot water. Ether and chloroform are good solvents for extracting the residue after the water has been removed.

The volatile compounds, which would be present in the distillate, will include the alcohols, esters, aldehydes, and ketones. If a test for aldehydes and ketones is positive, these classes may be separated from the alcohols and esters by conversion to the sodium bisulfite complexes or to the phenylhydrazones. The alcohols and esters may often be separated by fractional distillation. Another method is to "salt out" the alcohols and esters by saturating the solution with potassium carbonate, separating the alcohol-ester fraction by means of a separatory funnel or pipette,

and then adding a few grams of calcium chloride to the alcohol-ester fraction. After a few minutes, add just enough water to dissolve the salt. The alcohol will remain in solution with the calcium chloride, whereas the ester will separate. To recover the alcohol, saturate the salt solution with sodium sulfate and extract with ether.

Mixtures of Division H compounds. Many, but not all, of the amines of this class are volatile with steam. Hence, steam distillation is sometimes helpful in separating such mixtures. Fractional crystallization and, less often, fractional distillation may be used. Of course, benzene sulfonyl chloride or phthalic anhydride will react with the primary and secondary amines, but not with the tertiary amines. It is occasionally advisable to treat the amine mixture with one of these reagents and then extract the tertiary amine with ether. The derivatives of the primary and secondary amines may be separated by solubility differences. If it is necessary to recover the original amines, the derivatives may be hydrolyzed by prolonged refluxing with dilute hydrochloric acid.

Aromatic amines may be separated from many impurities by converting them into picrates in alcohol solution. The amines may be regenerated from the picrates by treatment with ammonia.

*Mixtures of Divisions **M**, **S**, and **I** compounds.* The scheme of separating mixtures proposed in this chapter places, in one residual group, all of the compounds that are soluble in ether but insoluble in water and were not extracted by hydrochloric acid or sodium hydroxide. There is, therefore, considerable probability that this residue will be a mixture of two or more compounds. If neither nitrogen nor sulfur are present in this residue, the Division **M** compounds are absent. In general, the Division **S** and Division **I** compounds are volatile with steam, whereas only a few Division **M** compounds are volatile with steam (*e.g.*, the chelated compounds like *o*-nitroaniline and *o*-nitrophenol). Hence, steam distillation will usually separate the Division **M** compounds from the other two classes.

Although sulfuric acid and phosphoric acid are not satisfactory for the separation of mixtures, the use of these acids is recommended for small samples to help in determining what types of compounds are present.

Division **I** compounds are insoluble in concentrated sulfuric acid. Of the compounds that dissolve in sulfuric acid, only the lower-molecular-weight ones will dissolve in 85 per cent phosphoric acid. It should be recalled that the members of these classes were removed by water extraction if they did not contain more than 4–5 carbon atoms per molecule. The phosphoric acid will dissolve members of these classes if they do not contain more than 8–9 carbon atoms per molecule.

Mixtures of Division **M** compounds may be best separated by fractional extraction or fractional crystallization. Mixed solvents are frequently useful. Several of the more common members of this class may be extracted by hot water, from which they will separate when the solution is cooled. Carbon tetrachloride will dissolve many of the compounds of Division **M** but it fails to dissolve many of the dinitro and polynitro compounds, anilides, amides, sulfones, and other compounds of similar structure. Chloroform will dissolve most of those compounds that are insoluble in carbon tetrachloride, especially if they contain active *donor* groups for hydrogen-bonding. Chloroform is not a good solvent for the sulfonamides. Methanol is useful in fractionating the mixture that is insoluble in carbon tetrachloride; it dissolves the anilides and amides but not the nitro compounds or sulfones. As previously mentioned, some few of the Division **M** compounds can be steam-distilled.

The mixtures of Division **S** and Division **I** compounds may frequently be fractionally distilled, either at atmospheric pressure or under vacuum. If aldehydes or ketones are present, the mixture may be dissolved in ether and extracted with a saturated solution of sodium bisulfite. For solid mixtures of these divisions, fractional crystallization from hot solvents is often the best method.

CHAPTER 15

Chromatographic Analysis[1]

CHROMATOGRAPHY is a method for the separation of compounds based on adsorption affinities. Different adsorption affinities cause the components to move down a column of adsorbent at different rates when washed by a solvent.

Apparatus and materials. The apparatus used for chromatography is very simple and may be easily improvised; however, the most suitable chromatographic tubes are specially constructed and are available commercially.[2] The tube bears on its lower end a ground-glass joint by which it is attached to an adapter, fitted with a perforated glass plate for supporting the adsorbent column. The parts of the chromatographic tube and the wooden stamper used to extrude the column from the tube are shown in Figure 65.

FIGURE 65
Chromatographic Tube and Wooden Stamper

A suitable adsorbent should have the following characteristics: (a) The rate of solvent flow through the adsorbent column should be about 10–50 mm per minute; (b) it should reversibly adsorb the substance to be chromatographed; and (c) it should not cause any chemical alteration of the compounds adsorbed.

In practice few really suitable adsorbents for chromatography are to be found. In many cases the rate of flow is so slow that it is necessary to "dilute" the adsorbent with a filter aid such as Celite or Hyflo Super-Cel.[3] This may have the disadvantage of causing the zones to be weak and spread out.

Alumina is one of the most widely used adsorbents but most brands are poorly adapted to chromatographic purposes. Materials such as "Neutrol Filtrol," silicic acid, silica-gel, calcium carbonate, calcium

[1] By Arthur L. LeRosen, Louisiana State University

[2] The tubes are manufactured by the Scientific Glass Apparatus Company, Bloomfield, N J

[3] Manufactured by the Johns-Manville Co ; also Dicalite, produced by the Dicalite Co

hydroxide, magnesium oxide, sugar, and the rest,[4] are generally more suitable for a given purpose.

Operation. A typical operation is carried out in the following way: A mixture of 2 pigments in a small volume of solution is poured on a vertical adsorbent column packed in a glass tube that is under suction; then the column is washed with pure solvent, called the *developer*. At first, both pigments are adsorbed in a narrow zone near the top of the column but, as washing proceeds, this zone becomes broader and separates into 2 zones, one for each of the pigments, which move down the column with different rates so that they become further separated as the development proceeds.

When a broad white interzone is formed between the pigment layers, the development is stopped. The suction is continued for a minute or two and the column is allowed to become dry. The tube is then taken off and placed on a table. The column is extruded by means of a stamper and the individual pigment zones are cut out separately. Each adsorbed pigment may be recovered by transferring its zone to a sintered glass funnel and washing it with a solvent that liberates the pigment from its adsorbate. This operation is known as *elution;* the solvent is termed an *eluent;* and the filtrate is the *eluate*. Evaporation of the solvent from such an eluate may yield the pure pigment as a residue. In this manner the constituents of the complex initial solution have been quantitatively separated and isolated.

Naturally, there are many modifications of the procedure described. For example, the individual zones may be gradually washed through the column and collected as separate filtrates. If the substances chromatographed are colorless, their zones must be located on the column by streak tests with a suitable color-forming reagent. Furthermore, the zones of some compounds fluoresce in ultraviolet light so that they may be easily detected.

The solvents used may be divided into two classes: the developers, used to differentiate the zones on the column, and the eluents, used to remove the substance from the adsorbate. Although chromatography may also be carried out with aqueous media, only nonaqueous solvents will be discussed.

As a rule the developers increase in strength as the polarity of the sol-

[4] The sources of some of these adsorbents are Neutrol Filtrol, The Filtrol Company, Los Angeles, Calif.; calcium carbonate, Merck heavy powder; silicic acid, Merck reagent; Micron brand magnesium oxide, Westvaco Chlorine Products Company, Newark, Calif.; calcium hydroxide, almost any commercial hydrated lime (some of the most suitable samples were certain batches of "Shell" brand lime from the Westvaco Chlorine Products Company).

vent molecule increases. As an example, the following solvents are listed in the order of their increasing strength as developers: ligroin, benzene, acetone. Sometimes mixtures of solvents are used as developers; for example, acetone-benzene, benzene-ligroin, and so on. A solvent may be a developer for one substance and an eluent for another.

When there are a number of zones on a column, it is generally possible to develop adequately only certain sections, so that a group of other zones may have to be rechromatographed by using another developer. Some of the developers that have been used in chromatography are ligroin, benzene, carbon disulfide, chloroform, carbon tetrachloride, 1,2-dichloroethane, acetone, ethanol, and others.

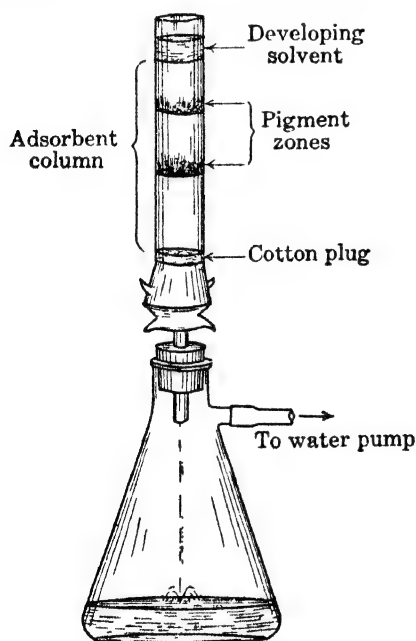



FIGURE 66
Standard Assembly of Chromatographic Apparatus

Eluents are usually polar solvents, such as ether, alcohol, or pyridine. The eluents may be used either undiluted or mixed with another solvent. Presumably, an eluent acts by displacing the adsorbed substance from the adsorbate. Eluents are often effective in very small amounts so that care must be taken to keep them out of the developing solvent. Typical eluents are methanol, ethanol, and ether.

In spite of the striking successes achieved by chromatography, it is not yet sufficiently appreciated by chemists. This lack of recognition may be due to some extent to the fact that the method is essentially empirical and is at present more of an art than a science. In order to appreciate its immense power as a means for separation of substances, one must become familiar with the characteristics of a satisfactory chromatogram.

It is certain that in each class of organic compounds many of the current techniques used in qualitative organic analysis will be replaced by chromatographic procedures. Therefore, a short discussion of this process will be included in the subsequent section, followed by two experiments designed for practicing the method. For a more detailed dis-

cussion, the reader should consult the several valuable references listed in the footnote.[5]

Procedure for chromatographic analysis. The chromatographic tube (Note 1) is attached to the suction flask by means of a rubber stopper, as shown in Figure 66 or Figure 67. The flask is connected to a water pump and the suction is turned on full. A plug of cotton is then inserted and pressed down with the stamper (Figure 65) so that it will form a support (about 3 mm thick) for the column (Note 2). The adsorbent powder is then poured into the tube through a powder funnel until the tube is about 5/6 full. The sides of the tube are tapped gently to settle the adsorbent and the top of the column is smoothed by moderate pressure with the stamper.

Next, the substance to be chromatographed is introduced into the column, dissolved in a small amount of solvent from which it is very strongly adsorbed (Note 3). Just as the last portion of this solution is disappearing into the adsorbent, a small amount of the developer is poured on the column (Note 4), followed by several smaller portions, until all of the solute has been washed into the adsorbent. Development is continued (Note 5) until the zones show the desired separation. The column is allowed to just become dry and the tube is removed from the adapter. The column is extruded as follows: the top and sides of the column are tapped against the palm of the hand several times in order to loosen it; then the tube is laid on a table and extruded by means of the stamper. In difficult cases the stamper may be supported against a block of wood resting on the operator's chest or stomach, while both hands are used to hold the tube and force out the column. The zones are cut out (Note 6) and eluted separately. Each is transferred to a sintered glass funnel and washed with the eluting agent until all the adsorbed substance is removed from the adsorbent. The eluate is then evaporated or worked up in

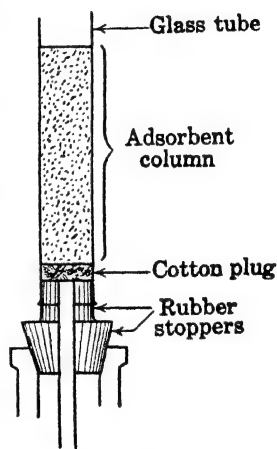



FIGURE 67

Alternative Assembly of Chromatographic Apparatus with Improvised Chromatographic Tube

[5] Zechmeister and L. Cholnoky, *Principles and Practice of Chromatography*, John Wiley and Sons, Inc., 2nd impression, New York, 1943; Strain, *Chromatographic Adsorption Analysis*, Interscience Publishers, Inc., New York, 1941; Alexander, *Colloid Chemistry, Theory and Methods*, **5**, 457–71 (1944), Reinhold Publishing Corp., New York; Lederer, *Bull. soc. chim.*, **6**, 897 (1939); Bersin, *Angew. Chem.*, **53**, 384 (1940); Strain, *Ind. Eng. Chem., Anal. Ed.*, **14**, 245 (1942).

some other manner. For example, the solution may be submitted to a spectroscopic test.

Separation of the carotenoid pigments of ripe tomatoes.[6] Fifty grams (Note 7) of tomato flesh (Note 8) is mashed in a mortar and ground to a pulp; 50 ml of methanol are added, and the grinding is continued for a few minutes. The suspension is then washed with 50 ml of methanol into a 300 ml wide-mouth glass-stoppered flask, and 100 ml of petroleum ether (b.p. 60–70°) are added. The mixture is shaken for 15 minutes by hand or on a shaker. The suspension is then filtered on a Buchner funnel by suction. The filtrate is saved and the solid fibrous residue is again ground up in the mortar and twice more submitted to the operations described. The final residue should be white.

The combined extracts are diluted with an equal volume of water in order to transfer the pigment to the petroleum ether, which forms a separate layer above the aqueous phase. The aqueous layer is removed in a separatory funnel and the upper (ligroin) layer is washed 8 times by short shakings with water (Note 9). It is then dried by standing over anhydrous sodium sulfate for a few minutes and filtered. This filtrate is evaporated down to about 20 ml before it is placed on the column.

A column of calcium hydroxide (Note 2), 230 mm long, is prepared in a chromatographic tube about 33 mm in diameter, according to the directions given in the preceding section. The pigment solution is poured on the column. Just as the last part is entering the adsorbent, a little petroleum ether is poured on, and this is repeated until all the pigment has passed into the adsorbent. The top of the column should never become dry. Next, the chromatogram is developed by ligroin until the lowest zone is about halfway down the column (Note 10). The same solvent, containing 10 per cent of acetone, is now poured on and the development is continued until the lowest zone is almost at the bottom of the column. At this point the column is allowed to just become dry. Air is allowed to enter the filter flask. The tube is removed and the adsorbent is extruded. The chromatogram usually shows a small red zone of lycoxanthine, $C_{40}H_{55}OH$, near the top of the column and, immediately below it, a broad red zone of the main pigment, lycopene, $C_{40}H_{56}$. The latter is followed by several small zones and then by a broad orange-colored β-carotene (a pro-vitamin A) zone. The lycopene and β-carotene zones are cut out separately with a scalpel and are eluted with ligroin containing 25 per cent alcohol. The eluates may be evap-

[6] This analysis is adapted from an article by Went, LeRosen, and Zechmeister, *Plant Physiology*, **17**, 91 (1942).

orated to dryness under reduced pressure (preferably after the alcohol has been washed out) to obtain the pure pigments.

Chromatographic separation of *o*-, *m*-, and *p*-Nitroaniline.[7] Three stock benzene solutions are made up, containing 5 mg per ml of *o*-, *m*-, and *p*-nitroaniline, respectively. A mixture of these solutions is prepared by mixing: 2 ml *ortho*-, 2 ml *para*-, and 4 ml *meta*-compound. A 1 ml sample of this mixture is used for the following experiment. Just before it is poured on the column, it is diluted to 5 ml with ligroin (b.p. 60–70°).

The adsorbent used is a mixture of 2 parts by weight of calcium hydroxide and 1 part of Celite; however, if the calcium hydroxide used shows a good rate of filtration, it need not be diluted with this filter-aid. A column about 150 mm long is prepared in a chromatographic tube, approximately 200 by 18 mm.

The benzene-ligroin solution is introduced and the chromatogram is developed with pure ligroin until the lowest zone is located about 1 cm from the bottom of the column. The column is allowed to become dry and is extruded. The position of the zones may vary with different brands of the adsorbent but the zones should be about as follows: (The first number designates the position of the top of the zone; the second, the bottom edge of the zone, measured from the top of the column; and the figure in parentheses gives the width of the zone. All are expressed in millimeters.) *p*-nitroaniline, 5–25 (20) bright yellow; *m*-nitroaniline, 65–90 (25), yellow; *o*-nitroaniline 95–145 (50), yellow. These zones may be cut out and eluted with benzene containing 10 per cent alcohol or with pure alcohol. Evaporation of each eluate should yield a pure compound.

Notes

1. For most purposes a chromatographic tube approximately 18 mm in diameter and 200 mm in length is suitable.

2. If the rate of filtration through the adsorbent is too slow, a filter aid should be used. The total time required for the development of the chromatogram should not exceed one hour. In many cases it is much shorter.

3. It is often convenient to prepare a concentrated solution of the substance in a solvent from which it is weakly adsorbed but readily soluble and then to dilute this solution with a solvent from which the com-

[7] These compounds were first separated by Karrer and Nielsen, *Trennung von Substanzgemischen in Chromatogramm und Ultrachromatogramm, Zangger-Festschrift,* Rascher and Company, Zurich, 1934, p 954.

pound is strongly adsorbed so that it forms a concentrated zone when poured on the column. The initial width of the zone of all the adsorbed substances on the column should not exceed one fifth of the length of the column.

4. The top of the column should never be allowed to become dry, since this often results in channeling and distortion of the zones.

5. The developer may be automatically fed into the column by placing it in an ordinary separatory funnel (the stopper should be wet with solvent to prevent entry of air); the stopcock is open; and the stem of the funnel extends inside the top of the chromatographic tube about 1–2 cm below the top edge.

6. The adsorbed zones are often concave at their bottom edge and convex at the top edge; consequently, it is not advisable to cut directly through the column at the edge of a zone, but rather to start from the top of the column and gradually slice the adsorbent off, holding the knife at an angle to the long axis of the column until a zone is reached. Then its contours are cautiously followed.

7. If it is desirable to use a chromatographic tube about 18 mm in diameter, the quantities of all materials given above that are used for the extraction of the tomatoes should be divided by 3.

8. If fresh tomatoes are not available, 10 g of tomato paste may be used instead. Other colored materials may be used; for example, carrots, green leaves, some colored flowers, fruit, and others.

9. A more efficient method of continuously washing out an eluting agent is described in the following article: LeRosen, Ind. Eng. Chem., Anal. Ed., **14,** 165 (1942).

10. If the column is examined in the dark under ultraviolet light when the development is about half complete, a strongly fluorescing zone may usually be observed below the lowest pigment zone.

Problems

It is the accepted practice for an instructor to develop problems that fit the particular needs of his students. For this reason, the problems presented in this Chapter should be regarded only as supplementary to those assigned by the instructor. To an industrial chemist, in particular, these problems may prove valuable in developing skill in the interpretation of experimental data. They will also serve as a review of many of the reactions.

In most cases, the problems set forth represent actual laboratory data obtained by students with commercial chemicals. The reader may assume that the compounds are organic, and that nitrogen, halogens, and sulfur are absent unless they are listed otherwise. The problem is to find the compound that will react in accordance with the data given.

1. A colorless, pleasant-odored liquid falls in Solubility Division **I.** A faint yellow color develops on the aluminum chloride in the test for cyclic structure. The boiling range of the compound is 109–111°. Nitration of the compound gives yellow crystals, which melt at 70°. The aroyl benzoic acid derivative melts at 136–7°.

2. A colorless liquid falls in Solubility Division **S.** The test for cyclic structure is negative. The compound fails to react with 2,4-dinitrophenylhydrazine and gives a negative test for active unsaturation. The original compound does not give the hydroxamate test for esters but, when the compound is treated with acetyl chloride, the product does give an ester test. The boiling range of the compound is 131–2°. It reacts with α-naphthyl isocyanate to form a derivative that melts at 68°.

3. A colorless liquid gives negative tests for active unsaturation and cyclic structure. It falls in Solubility Division **E.** It gives a weakly positive test with Schiff's reagent and gives a positive test with the iodoform reaction. The boiling point is 55–56°. The phenylhydrazone of the compound melts at 41–42°; the *p*-nitrophenylhydrazone melts at 148–9°.

4. A colorless liquid gives a faint yellow color to aluminum chloride. The solubility determinations seem to indicate a borderline case, with Divisions **S** and **I** as possibilities. The compound fails to react with phenylhydrazine or acetyl chloride. It gives negative tests in the

xanthate and hydroxamic acid reactions. Nitration with fuming nitric acid gives a yellow solid, which gives a test for a dinitro compound by the acetone-sodium hydroxide test. The original liquid boils at 79–80°, and the nitro derivative melts at 89°. The aroyl benzoic acid derivative melts at 127°.

5. A light yellow liquid gives a positive test for nitrogen. It falls in Solubility Division **M.** The test for cyclic structure is positive. The compound does not darken appreciably when treated with the acetone-sodium hydroxide reagent. It oxidizes ferrous hydroxide. The boiling point of the original liquid is 208–9°, and its nitration product melts at 89–90°.

6. A pinkish-tan solid gives negative tests for active unsaturation. It gives a purple color when tested for cyclic structure with aluminum chloride. It falls in Solubility Division **A.** The compound gives a red color with the ceric nitrate reagent and a purple coloration with ferric chloride. It also gives a purple color when treated with a mixture of sulfuric acid and sodium nitrite. The compound melts at 93–94° and gives a derivative with α-naphthyl isocyanate, which melts at 150–152°; its phenylurethan melts at 178°.

7. A slightly yellow liquid gives a positive test for halogen. Further tests show that the halogen is bromine. The compound falls in Solubility Division **I.** Only a small precipitate is obtained when the compound is shaken with alcoholic silver nitrate. The boiling point of the compound is 156–157°. When the compound is refluxed with metallic sodium, a white solid is formed that melts at 69°. This solid does not contain halogen and has a borderline solubility, being in Division **S** or Division **I.** The nitration product of this solid melts at 233°. Nitration of the original yields a product that melts at 75°.

8. A colorless solid falls in Solubility Division **C.** The test for cyclic structure is positive. It gives a wine coloration with ferric chloride. The melting point of the compound is 156–157°. When it is treated with thionyl chloride and then refluxed with aniline, the derivative melts at 133–134°. The anilide of the original compound melts at 135°.

9. A colorless solid gives positive tests for nitrogen and halogen. The cyclic test is positive and the compound falls in Solubility Division **H.** The precipitate is small when the compound is shaken with alcoholic silver nitrate. The melting point is 70°. The compound reacts with acetyl chloride and gives a derivative that melts at 178–179°. The original compound reacts with benzenesulfonylchloride to give a product that is soluble in sodium hydroxide solution and that melts at 122°.

10. A light tan liquid boils at 193–4°. It contains nitrogen. It gives

a positive cyclic test. It seems to partly dissolve in dilute acid but is placed in Solubility Division **M.** The compound reacts with nitrous acid solution to yield a yellow oil. It does not oxidize ferrous hydroxide. It reacts with benzenesulfonylchloride to form a solid that does not dissolve in aqueous sodium hydroxide. This solid melts at 79°.

11. A colorless liquid boils at 101–102°. The Solubility Division is **E.** The aqueous solution is neutral. The compound gives a positive test for alcohols by the xanthate test but, when the original compound is treated with acetyl chloride, the product that forms does not give a test for esters. This product falls in Solubility Division I and gives a test for chlorine. However, when the original compound is mixed with dimethyl aniline and then treated with acetyl chloride, an ester is formed. The 3,5 dinitrobenzoate of the original compound melts at 115–116°. The α-naphthyl urethan melts at 72°.

12. A colorless liquid falls in Solubility Division **E** and has a boiling point of 96–97°. It readily decolorizes a bromine solution. Its aqueous solution is neutral. It does not react with phenylhydrazine or ferric chloride. It gives a yellow precipitate when treated with solid sodium hydroxide and carbon disulfide. It fails to give a positive test in the hydroxamic acid reaction before treatment with acetyl chloride but does give a purple color after treatment with the acyl halide. The original compound reacts with 3,5 dinitrobenzoyl chloride to give a derivative that melts at 48°. The phenyl urethan melts at 70°.

13. A colorless liquid that boils at 74° is soluble in both water and ether. The compound reduces an alkaline solution of cupric ions and gives a light red coloration with Schiff's reagent. The compound reacts with 2,4 dinitrophenylhydrazine to give a reddish-orange solid that melts at 122°. The semicarbazone melts at 106°.

14. A white solid contains halogens and falls in Solubility Division **I.** Nitration of the compound gives a light yellow solid that melts at 84°. The original compound melts at 89°.

15. A colorless compound melts at 48–49°. It is soluble in sulfuric acid but not in the other solvents. The compound does not react in the xanthate test or in the hydroxamic acid test. It gives a test for cyclic structure but does not contain active unsaturation. When the compound is fused with sodium hydroxide, a liquid distils that has a boiling point of 80°. The fused mass is dissolved in water and acidified and at that point a solid precipitates that is found to be in Solubility Division **C** and to have a melting point of 121°. The original compound forms a phenylhydrazone that melts at 137° and a semicarbazone that melts at 167°.

16. A yellow solid contains nitrogen. It dissolves in sodium bicarbonate with difficulty but is placed in Division **C**. It gives a purple color with ferric chloride and a yellow-orange color with the acetone-sodium hydroxide reagent. It oxidizes ferrous hydroxide readily and decolorizes a bromine solution. The bromination product melts at 118°. The nitration product of the original compound melts at 121–122°. The original compound melts at 114°.

17. A gray-green solid melts over the range 110–120°. The material is recrystallized from an alcohol-water mixture to yield colorless crystals that melt at 123–125°. Nitrogen and sulfur are found present. The compound is insoluble in water and acid but reacts with 10 per cent sodium hydroxide solution to form colorless crystals that melt at 54° and contain nitrogen but no sulfur. No organic sulfur compounds can be found in the alkaline solution but it is noted that, when the solution is acidified with hydrochloric acid and barium chloride is added, a white precipitate forms. When the crystals forming when the original compound is treated with sodium hydroxide are refluxed with acetyl chloride, a solid forms that melts at 101°.

18. A yellow solid contains nitrogen and chlorine. It gives a positive test for cyclic structure and falls in Solubility Division **M**. It gives a moderate precipitate when treated with an alcoholic solution of silver nitrate and readily forms silver chloride after treatment with an alcoholic solution of potassium hydroxide. The compound oxidizes ferrous hydroxide but fails to change the color of the acetone-sodium hydroxide reagent. The compound melts over the range 45–47°. The compound is refluxed for 3 hours with an alkaline solution of potassium permanganate. The manganese dioxide is filtered off and the filtrate is acidified. A white precipitate forms that contains nitrogen but not halogen. This precipitate falls in Solubility Division **C** and melts at 140–141°. This derivative forms an anilide that melts at 143°.

19. A white solid melts at 114° and contains nitrogen. It falls in Division **M**. It does not oxidize ferrous hydroxide. When the compound is strongly heated with soda-lime, a liquid distils. This liquid is found to contain nitrogen and to fall in Solubility Division **H**. The reaction of this liquid with acetyl chloride gives the original starting material.

20. A white crystalline solid contains nitrogen. The melting point is 114° and the Solubility Division **W**. The aqueous solution is neutral to litmus. When the solid is heated, it distils at 222°. Water is evolved during this distillation. This distillate reacts with nitrous acid to form a water-soluble acid that boils at 118°.

21. A liquid contains sulfur and falls in Solubility Division **M.** The compound is oxidized to a white solid that melts at 128–129°. When the original compound is heated with a mixture of concentrated nitric and sulfuric acids, it yields a solid that melts at 201°.

22. A solid of Solubility Division **C** is found to contain nitrogen, sulfur, and halogens. The melting point is 80°. When an alkaline solution of the compound is acidified, a solid is recovered that contains nitrogen and sulfur but no halogens. This compound melts at 109–11°. The original compound reacts with aniline to give a compound which melts at 171° and is soluble in 10 per cent sodium hydroxide. The amide melts at 180°.

23. A colorless liquid boils at 83–84°. It adds bromine rather readily and reacts with concentrated sulfuric acid (darkens). The original compound is refluxed with an alkaline solution of potassium permanganate. During this treatment, the compound goes into solution. Acidification of the aqueous solution causes a white precipitate to form. This new compound is found to fall in Solubility Division **C** and to melt at 152–154°. A saturated solution of this oxidation product is found to be definitely acidic. The solid acid is distilled with solid barium hydroxide to yield an oily liquid that distils between 125° and 130°. This liquid falls in Solubility Division **S** and forms a semicarbazone that melts at 210°.

24. How could the following binary mixtures be most readily separated, keeping in mind the necessity for having each component pure enough for the preparation of a derivative?

a. Benzoic acid and dextrose.
b. *o*-Nitrophenol and *p*-nitrophenol.
c. *m*-Nitrotoluene and *m*-chloroaniline.
d. *m*-Toluidine and N-ethyl-N-methylaniline.
e. Benzene and cyclohexane.

25. Outline a scheme for the separation of the following mixtures, and give the equations for the preparation of satisfactory derivatives for each component:

a. Acetone, aniline hydrochloride, oxalic acid, 2-butanol, *p*-nitrobenzoic acid, α-naphthol, dinitrobenzene, and benzyl alcohol.
b. *o*-Nitroaniline, dimethylaniline, nitrobenzene, benzylcyanide, diphenyl, diphenylsulphone, glycerol, and benzene.
c. Chloroacetic acid, acetic acid, acetone, ethyl propionate, phenol, and benzaldehyde.

26. Make up problems similar to those in this chapter for each of the following compounds: propyl iodide, butanone, pentanal, 3-aminophenol, anthracene, propionic anhydride, ethyl propionate, benzamide, thiophenol, 2-nitrotoluene, cinnamic acid, hydroquinone, diphenylamine, phthalic anhydride, phenyl cyanide, dextrose, benzene sulfonic acid, *p*-phenylenediamine, 2-nitropropane, and 8-hydroxyquinoline.

PART II

Tables

Tables

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Preface to Tables

Compounds melting above 20° are classed as solids and are arranged according to increasing ***melting points.*** Compounds melting below 20° are arranged according to increasing ***boiling points.***

Compounds that have a boiling point only under reduced pressure (unless boiling under slight decomposition at atmospheric pressure) are listed as liquids distilling only under reduced pressure.

An asterisk following the melting point or boiling point of a derivative indicates that the value is corrected.

x- used before a derivative indicates that the position of the substituent in that derivative is unknown. For example *x*-dibromo . . . indicates that the positions of the two bromine atoms in the derivative are not known.

Where two melting points or more exist for a derivative the values are connected by the word *and;* thus, *118 and 145* indicates that the particular derivative exists in two forms, one that melts at 118° and another at 145°. On the other hand there are many derivatives for which several melting points are listed in the literature; in some cases, besides the value selected for the Tables in this book, one or two additional values have been listed in parentheses to the right or under the selected value. For a more elaborate discussion of this topic see pages 201–204.

The reader should consult pages 195–201 with reference to the selection of the derivative to be prepared.

In case the available data indicates a particular compound and the prepared derivative does not give the melting point listed in the Tables, the reader should consult page 204.

Wherever a reference number appears in the Note column of a table, the note to which the number refers will be found below the last table in the group within which the table is included.

For easier reference and also for identification in the index, numbers appear in sequence (1, 2, 3, etc.) at the left of the names of the compounds listed in the left column of each table. Whenever a table continues across two facing pages, the names of the compounds are omitted on the second page, but the numbers are repeated.

List of abbreviations. As far as possible the abbreviations used in the explanatory notes on the compounds listed in the Tables conform to those used in the chemical abstracts. This plan holds true particularly for the chemical abbreviations used in Table No. 42 on miscellaneous compounds. Thus, for example, MeOH stands for methanol, EtOH for ethanol, Ac_2O for acetic anhydride, Et_2O for ether, and so forth. No attempt is made in the

following list to give explanations of the chemical abbreviations because it is assumed that the reader is already familiar with them. The abbreviations are those commonly used for words or sentences in these tables.

acc.: according
addn.: addition
alc.: alcohol(ic)
alk.: alkali(ne)
amm.: ammonia, or ammonium
anh.: anhydrous
approx.: approximate(ly)
aq.: aqueous
arom.: aromatic
at.wt.: atomic weight
b: boils (at)
B.P. or **b.p.**: boiling point
Cf.: compare or consult
compd.: compound
conc.: concentrated
concn.: concentration
cryst.: crystalline; crystals
D: density
d: decomposing
dec.: decomposes
decompn.: decomposition
deliq.: deliquescent
deriv.: derivative
detn.: determination
diffn.: differentiation
dil.: dilute
diln.: dilution
esp.: especially
et al.: and others
evap(d).: evaporate(d)
evapn.: evaporation
exc.: except
hr(s).: hour(s)
hyd.: hydrated
ident.: identification
immed.: immediately
insol.: insoluble
liq.: liquid
m: melts (at) or melting point
max.: maximum
min.: minimum
min(s).: minute(s)
mol.: molecular, molecule
M.P. or **m.p.**: melting point
mxt.: mixture
N (after the boiling point, or melting point): Indicates a note to be found at the end of the group of compounds, in which this particular compound appears. The reference number for the note will be found in the column headed "Note," except where it immediately follows N.
org.: organic
oxdn.: oxidation
phys.: physical
pol.: polymerises readily.
ppn.: precipitation
ppt(s).: precipitate(s)
pptd.: precipitated
pr.: pressure
prepd.: prepared
prepn.: preparation
qu.: quantity
qual.: qualitative
quant.: quantitative
red.: reduced
redn.: reduction
ref(s).: reference(s)
s: sublimes
sat.: saturated
sl.: slightly
sol.: soluble
soln.: solution
spar.: sparingly
subl.: sublimes
temp.: temperature
T.S.: test solution
uncorr.: uncorrected
unsym.: unsymmetrical

v or **vol(s).**: volume(s)
v.s.: volatile with steam
vac.: vacuum (or reduced pressure)
x: Used before a derivative to indicate that the position of the substituent in that derivative is unknown.
yel.: yellow
! (after figures): Indicates accuracy.
→: Indicates that such treatment gives compound following arrow.

Corrected m.p. or b.p. is marked by asterisk, thus 177*. The degree sign is usually omitted after the figures denoting *m.p.* or *b.p.* (or *m* or *b*). An exclamation point indicates that several values were found and the one so designated was chosen as the most reliable. Brackets [ ] indicate that the derivative has been prepared only indirectly.

In the case of addition compounds or salts with HCl and the like, the base or compound to be identified is indicated by its initial letter (capital) followed by a center dot to separate it from the rest of the addition compound, a subscript, if necessary, being added to show the number of molecules involved; thus, $E \cdot HCl$ listed under ephedrine denotes ephedrine hydrochloride and $P_2 \cdot H_2SO_4$ under physostigmine denotes the physostigmine sulfate with two molecules of the base.

Literature references. General references which the reader may use for further consultation for derivatives and their constants are listed on pages 154–157. Selected references to current literature appear at the end of each section on the preparation of derivatives in Chapters 9–13.

TABLE 1

Acids (Liquid above 20°)

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C): Recommended: *p*-Toluidide	Recommended: Anilide	Others: *p*-Nitrobenzyl ester	Others: *p*-Phenylphenacyl ester
1	Thioacetic		93	130	76		
2	Formic	1	101	53	50	31	74
3	Acetic	2	118	147 (153)	114	78	111
4	Acrylic	3	140	141	105		
5	Propionic	4	141	124	105 (103)	31	102
6	Propiolic	5	144*d*		87		
7	Isobutyric	6	155	107 (104)	105		89
8	Methacrylic	7	163				
9	Pivalic (Trimethylacetic)		164	120	133		
10	*n*-Butyric		165	75 (72)	96 (92)	35	82
11	Pyruvic	8	165*d*	[130]	[104]s		
12	Isocrotonic (*cis*)	9	169 (165*d*)	132	102		
13	Vinylacetic (3-Butenoic)	10	169		58		
14	Isovaleric	11	176	107	110		78
15	*dl*-2-Methylbutanoic	12	176	93	110		71
16	3,3-Dimethylbutanoic	13	184	134	132		92
17	Chloroacetic, *m.p* 63		185		134		116
18	*dl*-α-Chloropropionic		186	124	92		
19	*n*-Valeric (Pentanoic)	14	186	74	63		63
20	2,2-Dimethylbutanoic		187	83	92		87
21	*dl*-2,3-Dimethylbutanoic		192	113	78		74
22	Dichloroacetic	15	194 (190)	153	121 (118)		
23	2-Ethylbutanoic (Diethylacetic)		195 (193)	116	127		77
24	*dl*-2-Methylpentanoic		196	81	95		64
25	*dl*-3-Methylpentanoic		197	75	87		47
26	4-Methylpentanoic (Isocaproic)		200 (198)	63	112		70
27	Methoxyacetic	16	203		58		
28	α-Bromopropionic	17	205	125	99		
29	Caproic (Hexanoic)	18	205	75	96		65
30	Ethoxyacetic		207	[32]			
31	2-Ethylpentanoic		209	129	94		
32	2-Methylhexanoic		210	85	98		
33	2-Bromobutanoic (β-Bromobutyric)		217*d* (122_{16})	92	98	49	
34	4-Methylhexanoic	19	218		77		
35	Heptanoic		223 (239)	81	70		62
36	2-Ethylhexanoic (α-Ethylcaproic)		228				54
37	Hexahydrobenzoic		233		146		
38	Caprylic (Octanoic)	20	239	70	57		67
39	α-Bromocaproic		240				
40	Levulinic		246	109	102	61	
41	Pelargonic (Nonanoic)	21	254	84	57		71
42	Undecylenic	22	275				
43	Undecanoic (*m.p.* 29) (Undecylic)	23	280	80	71		80
44	Oleic	24	dec.	43	41		61
45	*dl*-Lactic (*m.p.* 16)	25	dec.	107	59		145

TABLE 1—*Continued*
Acids (Liquid above 20°)

	MELTING POINT OF DERIVATIVES (°C)—*Continued*							
	Others (Continued)							
	p-Chloro-phenacyl ester	*p*-Bromo-phenacyl ester	Amide	*p*-Bromo-anilide	Methylene-bisanilide	Benzimi-dazole	Phenyl-hydrazide	Others
1			108 (115)					Hydrazide, 59 *p*-Aniside, 114
2	128	140		119		173	143*d*	
3	72	86	82	168	228		129	
4			85					
5	98	63	81	149	213	175	157	
6			62					
7		77	129	155		224	140	
8			102-6	116				Ureide, 143
9		76	154					
10	55	63	115	115	198	157	102	
11			[125]	168				Phenylhydrazone, 159 and 150
12		81	102					
13			73					
14		68	135	128		187		
15		55	112	122				
16			132					
17			120			111		
18			80					
19	98	75	106 (108)	108	189	155	109	
20			103					
21			132					
22		99	98					
23			112					
24			80					
25			125			159		
26		77	120				144	
27			97	85		136		
28			123					
29	62	72	101	105	186	163	98	
30	94	105	82					
31			105	148				
32			72	114				
33			112					
34			98					
35	65	72	96	98	184	138	103	
36								
37			186					
38	63	67	106	103	183	145	106	
39								
40		84	108*d*					
41	59	68	99	100	177	140		
42			87				97	
43	62	68	103	102		114	110	
44	40	46	76					
45		113	79			179	115	

TABLE 2
Acids (Solid)

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C)			
				Recommended		*Others*	
				p-Toluidide	Anilide	*p*-Nitrobenzyl ester	*p*-Phenylphenacyl ester
1	2-Bromobutanoic b_{16} 122° (β-Bromobutyric)		20				
2	Hexahydrobenzoic	26	30-31		146!		
3	Capric (Decanoic) *b* 268.7	27	31	78 (73)	70		
4	3-Bromobutanoic (γ-Bromobutyric)		33				
5	Levulinic	28	33	109	102	61	
6	Erucic		34	[58]	55		76
7	Trimethylacetic	29	35	[120]	[132]		
8	Tridecanoic		41	88	80		87
9	Lauric	30	42	87 (82)	78		86
10	α-Bromoisovaleric		44				
11	Elaidic		44-45				73.5
12	Angelic	31	45		[126]		
13	Hydrocinnamic	32	49	135	96	36	95
14	α-Bromoisobutyric		49				
15	Bromoacetic		50		131	88	
16	γ-Phenylbutyric		52				
17	Pentadecanoic		52		78	40	92
18	Myristic (Tetradecanoic)		54	93	84		90
19	Trichloroacetic		57	113	94	80	
20	Brassidic		60		78		86
21	Margaric (Heptadecanoic)		61			49	96!
22	β-Bromopropionic		62.5				
23	Palmitic (Hexadecanoic)		63	98	91	42	94
24	Chloroacetic		63		134		116
25	α, β-Dibromopropionic		64				
26	Tiglic	33	65	70-71.5	77	64	
27	Cyanoacetic		66		198		
28	*d*-Chaulmoogric	34	68.5	100	89		
29	Stearic (Octadecanoic)		70	102	95		97
30	α-Crotonic (*trans*-)	35	72	132	118	67	
31	Phenylacetic	36	76.5	136	118	65	63*d*
32	Arachidic (*b* 328)		77	96	92		86
33	Glycolic	37	79	143	97	107	
34	α-Hydroxyisobutyric		79	133	136	80	
35	Iodoacetic		84		143		
36	Citraconic	38	92		175	71	
37	Glutaric	39	98	218	224	69	152
38	Phenoxyacetic		99		99		
39	Citric (monohydrate)	40	100	189	199	102	146
40	*o*-Methoxybenzoic		100-101		(62)		131
41	Oxalic (dihydrate)	41	101	268	246	204	166*d*
42	*o*-Toluic	42	104	144 (142)	[125]	91	94.5
43	Pimelic	43	105	206	155		148*d*
44	Azelaic	44	106	201	186	44	141
45	*m*-Toluic	45	110	118	126	87	136.5
46	Ethylmalonic		111		150	75	
47	Pyrotartaric		115	164 (mono)	200		
48	Benzylmalonic		117*d*		217	119	

TABLE 2—*Continued*

Acids (Solid)

	MELTING POINT OF DERIVATIVES (°C)—*Continued*							
	Others (*Continued*)							
	p-Chlorophenacyl ester	*p*-Bromophenacyl ester	Amide	*p*-Bromoanilide	Methylene-bisanilide	Benzimidazole	Phenylhydrazide	Others
1			93					KOHaq → Crotonic
2			186					
3	62	67	100	102		127	105	
4								Lactone, m. 48
5		84	108*d*					
6	56	62.5	84					
7		76	154					
8		75	100					
9	70	76	100	104		107!		
10			133					
11		65	89-90					
12			127-128					
13		104	105			186		
14			148					
15			91					
16			84					
17		77	102					
18	76	81	103	107		105!		
19			141				123	
20	69	74	94					
21	79	83	106			94!		
22			111					
23	82	86	105	110		97	111	
24			120				111	
25			130					
26			76					
27			123					
28			106					
29	86	90	109 (114)	114			115	
30		96	161.5					
31		89	156			187	175	
32	86	89	108-9					
33		138	120			172		
34			98					
35			95					
36			187*d* (diamide)					
37		137	175-176					
38		148	101					
39		148	210-215*d*					
40		113	129					
41			419*d*					
42		57	143 (158)					
43		137						
44		131	172					
45		108	94					
46			214					
47			225					
48			225					Phenacyl ester, 101.5

TABLE 2—Continued

Acids (Solid)

	Name of Compound	Note	M. P (°C)	Melting Point of Derivatives (°C)			
				Recommended		Others	
				p-Toluidide	Anilide	*p*-Nitro-benzyl ester	*p*-Phenyl phenacyl ester
49	Tropic		117-118				
50	Mandelic		118	172	152	124	
51	Benzoic	46	121.7	158	160	89	167
52	Picric (see Table of Phenols)		122 5				
53	Trichlorolactic		124		164		
54	3-Nitrosalicylic (hydrated)		125				
55	Diethylmalonic		125				
56	*o* Benzoylbenzoic		128		195	100	
57	Thiobenzoic		130 (224)	129	102 (96)		
58	Maleic	47	130	142	187	91'	168
59	α-Naphthylacetic		131		155		
60	Furoic (Pyromucic)	48	133-4	107 5	123 5	133 5	
61	Sebacic		*s* 133	201	201	73	140
62	Cinnamic	49	133	168	151 (153)	117	182
63	Malonic	50	135! (133*d*)	253	228	86	175
64	Acetylsalicylic		135		136	90 5	
65	Methylmalonic		135*d*	228	182		
66	Phenylpropiolic	51	137	142	128	83	
67	*o*-Chlorobenzoic		140		114	106	
68	*m*-Nitrobenzoic		140		154	141	
69	*meso*-Tartaric	52	140				
70	Suberic		141	218	186	85	151
71	3-Nitrosalicylic		144				
72	Anthranilic (see Table of Amino Acids)		145 (147)				
73	*o*-Nitrobenzoic		146		155	112	
74	Diphenylacetic		148	[173]	180		111
75	*o*-Bromobenzoic		150		141	110	
76	Benzilic	53	150	[190]	[175]	99.5	122
77	Citric (anhydrous)	40	153	189	199	102	146
78	*p*-Nitrophenylacetic		153				
79	2, 5-Dichlorobenzoic		153				
80	Adipic		154!	241	241	106	148
81	*m*-Bromobenzoic		155		146	105	
82	*m*-Chlorobenzoic		158		122	107	
83	Salicylic	54	159.8		136 (135)	98	148
84	α-Naphthoic		162		163		
85	*o*-Iodobenzoic		162		141	111	143
86	3, 4-Dimethylbenzoic		164				
87	4-Nitrophthalic		165	172 (mono)	192		
88	Itaconic	55	165		185N	91	
89	Mesitylenic		166				
90	*d*-Tartaric	52	170		264	163	
91	*m*-Aminobenzoic (see Table of Amino Acids)		174				
92	3, 5-Dinitrosalicylic (hydrate)	56	174				
93	*p*-Toluic	57	178	160	145	104.5	165
94	Veratric (anhydrous)		181		154		
95	3, 5-Dinitrosalicylic anh.	56	182				
96	2, 4-Dinitrobenzoic		183			142	
97	*p*-Anisic	58	184	186	169	132	160
98	β-Naphthoic		184	192	171		
99	Succinic	59	185 (189)	255	230	88	208

TABLE 2—*Continued*

Acids (Solid)

	MELTING POINT OF DERIVATIVES (°C)—*Continued*							
	Others (*Continued*)							
	p-Chlorophenacyl ester	*p*-Bromophenacyl ester	Amide	*p*-Bromo anilide	Methylene-bisanilide	Benzimidazole	Phenylhydrazide	Others
49			169					
50			132			202		
51	119	119	130				168	
52								
53			145				123	
54			145					
55			224 [b p 360] s					
56			165'					
57								
58			181					
59			181					
60		138 5	143					
61		147	210				194	
62		146	148 (142)					
63			170				194	
64			138					Phenyl ester, 105
65			217					
66			100					
67		106	139 (142)					
68		132	143					
69			190				[245]	
70		144	217					
71			145					
72								
73		107	176					
74			168					
75			155					
76		152						
77		148	210-15*d*					
78		207	198					
79			155					
80		154 5	220				209	
81			155					
82		116	134					
83		140	142 (139)					
84		135 5	202					
85		110	184					
86			130					
87			200*d*					
88		117	192					
89			133					
90		204	196*d*				240	
91								
92			181					
93		153	160 (166)					
94			164					
95			181					
96		158	203					
97		152	167					
98			195					Methyl ester, *m* 77
99	196	211	260				210	

TABLE 2—*Continued*

Acids (Solid)

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C)			
				Recommended		*Others*	
				p-Toluidide	Anilide	*p*-Nitrobenzyl ester	*p*-Phenylphenacyl ester
100	*p*-Aminobenzoic (see Table of Amino Acids)		186				
101	Hippuric		187		208	136	
102	*d*-Camphoric		188		(di-) 226	66.5	
103	Aconitic	60	191*d*				
104	Dimethylmalonic		193*s*				
105	Glutamic (see Amino Acids)		199 (192)				
106	*m*-Nitrocinnamic		199			174	
107	Protocatechuic		200*d*		166	188	
108	*m*-Hydroxybenzoic	61	200	163	157	106-8	
109	3, 5-Dinitrobenzoic		202		234	157	154
110	Mesaconic	62	204.5!	212	186	134	
111	*dl*-Tartaric (Racemic monohydrate)	52	204		236	148	
112	*dl*-Tartaric (anhydrous)		206				
113	*p*-Coumaric		206				
114	Phthalic	63	206*d* (200)	201 (150)N	253.5 (170)N	155	167
115	Vanillic		207			140	
116	*o*-Coumaric	64	208			152.5	
117	*p*-Hydroxybenzoic	65	210	204	197	180-2	240
118	*β*-Resorcylic (2, 4-Dihydroxybenzoic)		213			189	
119	Mucic	66	214*d*			310	149.5*d*
120	Piperic		216			145	
121	3-Nitrophthalic		218		234	189	149
122	2, 4, 6-Trinitrobenzoic		220*d*				
123	2-Hydroxy-3-naphthoic		223!*	222	249!*		
124	5-Nitrosalicylic		227		224		
125	Diphenic		229		230	187	
126	Nicotinic	74	237-8*s* (228)	150	85		
127	*o*-Nitrocinnamic		240			132	146
128	*p*-Nitrobenzoic		241 (238)		204	168	182
129	*p*-Chlorobenzoic		242		194	129	160
130	Barbituric (see Table 42)		245*d*				
131	1-Hydroxy-3-naphthoic		249		113!	164	
132	Tetrachlorophthalic		250*d*			180	
133	*p*-Bromobenzoic		251		197	139	160
134	Gallic	67	254*d*		207		195-8*d*
135	*p*-Nitrocinnamic		285			186	192
136	Muconic		289*d*				
137	Fumaric	68	295*s* (287)		314	151	
138	Terephthalic	69	300!*s*		334-7	263	
139	Isophthalic	70	348*s*			202	
140	Trimesic	71	380! (375)		[118*d*]		
141	Uric	74	400*d*				

TABLE 2—*Continued*

Acids (Solid)

	Melting Point of Derivatives (°C)—*Continued*							
	Others (Continued)							
	p-Chloro-phenacyl ester	*p*-Bromo-phenacyl ester	Amide	*p*-Bromo-anilide	Methylene-bisanilide	Benzimi-dazole	Phenyl-hydrazide	Others
100								
101		151	183					
102			[193]					
103		186						
104			269					
105								
106		173	196					
107			212					
108		176						
109			183					
110			177					
111			226					
112								
113			194					
114		153	149(mono) 220(di)					
115								
116			209*d*					
117		191.5						
118			222					
119		225						
120								
121			201					
122			264*d*					
123			218!*					
124			225					
125			212					
126			128					
127		141	185					
128		137	201					
129			179					
130								
131			209-211!					
132								
133			189					
134			245					
135			204					
136			240*d*					
137			266*d*					
138		225						
139		179	280					
140			365 *d*					
141								

TABLE 3
Acid Anhydrides

	Name of Compound	Note	B. P. (°C)	M. P. (°C)	Melting Point of Derivatives (°C)				
					Acid		Amide	Anilide	p-Toluidide
					B. P. (°C)	M. P. (°C)			
1	Acetic		140	−73	118	16.6	82	114	147
2	Propionic		166	−45	141	—	81	105	124
3	Isobutyric		182 5		155	—	129	105	107 (104)
4	Butyric		198		165	—	115	96 (92)	75
5	γ-Butyrolactone	72	206						
6	γ Valerolactone		207						
7	Citraconic		214	8	—	92	187	175	
8	Valeric		218		186	—	106 (108)	63	74
9	Caproic		245	−41	205	—	101	96	75
10	Crotonic		248		—	72	161.5	118	132
11	Heptanoic (Enanthic)		258 (164/12.5mm)	17	223	−12	96	70	81
12	Caprylic		280-5/5mm	−1	239	16.3	106	57	70
13	Capric			24	268 7	31 3	100	70	78
14	Lauric			41 8		42	100	78	87
15	Benzoic		360	42		121.7	130	160	158
16	Maleic		202 (199)	56 (52)		130	181	187	142
17	Myristic			53.4		54	103	84	93
18	Palmitic			63 4		63	105	91	98
19	Itaconic	55		67-8		165	192	185N	
20	Stearic			71 5		70	109 (114)	95	102
21	3,5-Dinitrobenzoic			109		202	183	234	
22	4-Nitrophthalic			119		165	200*d*	192	
23	Succinic		261 (250)	120 (116)		185	260	230	255
24	Cinnamic			130		133	148	151 (153)	168
25	Phthalic	63	295 (284)	131.6		206*d* (200)		254	220
26	3-Nitrophthalic			162		218	201	234	
27	1,2-Naphthalic			169		175*d*	265*d*		
28	p-Nitrobenzoic			189		241 (238)	201	204	
29	d-Camphoric			221		188	193	226	
30	Tetrachlorophthalic			256 (249)		250*d* (256)			214 5 (207)
31	2,3-Naphthalic			266		241*d*			
32	α-Naphthoic			274		162	202	163	
33	1,8-Naphthalic	73		274		274*d*	300N	202N	
34	Tetrabromophthalic			275		266			
35	Tetraiodophthalic			318		327			

TABLE 4
Acid Halides[a]

	Name of Compound	M. P. (°C)	B. P. (°C)	Melting Point of Derivatives (°C)		
				Amide	Anilide	Others
1	Acetyl chloride		55	82	114	
2	Oxalyl chloride		64	419*d*	246	
3	Acrylyl chloride		76	85	105	
4	Propionyl chloride		80	81	105	
5	Acetyl bromide		81	82	114	
6	Isobutyryl chloride		92	129	105	
7	Butyryl chloride		100	115	96 (92)	
8	Chloroacetyl chloride		105	120	134	
9	Dichloroacetyl chloride		107	98	121 (118)	
10	Isovaleryl chloride		115	135	110	
11	Trichloroacetyl chloride		115	141	94	
12	Crotonyl chloride		126	161.5	118	
13	Valeryl chloride		127	106 (108)	63	
14	Chloroacetyl bromide		127	120	134	
15	Isocaproyl chloride		144	120	112	
16	Bromoacetyl bromide		149	91	131	
17	α-Bromopropionyl bromide		153	123	99	
18	Caproyl chloride		153	101	96	
19	Succinyl chloride	16	190*d*	260	230	
20	Heptanoyl chloride		193 (175)	96	70	
21	Caprylyl chloride		196	106	57	
22	Benzoyl chloride		197	130	160	
23	Phenylacetyl chloride		210	156	118	
24	Pelargonyl chloride (Nonanoyl)		215.3	99	57	
25	Benzoyl bromide		218	130	160	
26	*p*-Chlorobenzoyl chloride	16	222	179	194	
27	*m*-Chlorobenzoyl chloride		225	134	122	
28	Decanoyl chloride (*b* 114/15mm)		232	100	70	
29	*o*-Chlorobenzoyl chloride		238	142	114	
30	*o*-Methoxybenzoyl chloride		254	128	62	
31	Phthalyl chloride	14	276 (280)	220 (149)	253-5 (170)	
32	*m*-Nitrobenzoyl chloride	35	278	143	154	
33	Lauryl chloride	−17		100	78	
34	Myristyl chloride (*b* 168/15mm)	−1		103	84	
35	Palmityl chloride	12		105	91	
36	*p*-Chlorobenzoyl chloride	16	222	179	194	
37	Succinyl chloride	16	190	260	230	
38	Salicylyl chloride (*b* 92/15mm)	18		142 (139)	136	
39	*o*-Nitrobenzoyl chloride	20		174	155	
40	Stearyl chloride	23		109	95	
41	*p*-Anisyl chloride	26 (23)		163	169	
42	*m*-Nitrobenzoyl chloride	35	278	143	154	
43	Cinnamyl chloride	36		148	153	
44	Phenacyl bromide (140/12mm)	51				Oxime, 89.5 (97) Semicarbazone, 156 (146)
45	Phenacyl chloride	59	247 (244)			Oxime, 89.5 Semicarbazone, 156
46	3,5-Dinitrobenzoyl chloride	74 (69)		183	234	
47	*p*-Nitrobenzoyl chloride	75		201	204	
48	Picryl chloride (see Table of Nitro Compounds)	83				
49	Diphenylcarbamyl chloride	86				

[a] For Sulfonyl Chlorides, see table, page 442.

1. Decomposed by conc. H_2SO_4.
2. M.P. 16.6.
3. M.P. 13. Polymerizes, esp. when warmed.
4. Salted out by $CaCl_2$.
5. M.P. 18. Na amalgam reduces it to propionic.
6. Odor of rancid butter.
7. M.P. 16. Polymerizes on repeated distillation.
8. M.P. 13.6. Violet-blue color with nitroprusside.
9. M.P. 15.5. Sharp odor.
10. Odor of butyric acid.
11. Offensive odor like decayed cheese.
12. Odor similar to preceding, but weaker.
13. B.P. at 741 mm.
14. Same odor as isovaleric.
15. M.P. 5–6; F.P. 11. Ethyl ester: B.P. 158.
16. Viscous, oily.
17. M.P. 24.
18. Oily; odor unpleasant; v.s.
19. B.P. at 754 mm.
20. M.P. 16.
21. M.P. 12.3.
22. M.P. 24.5. Cu salt: M.P. 232–4; Pb salt: M.P. 80.
23. M.P. (α): 13.4; (β): 16.3.
24. B.P. 285-6/100 mm; M.P. 14.
25. M.P. 16.8.
26. B.P. 233. Penetrating, and persistent fecal odor.
27. B.P. 269.
28. B.P. 246 undecomposed. Often deliquesces to a liquid at ordinary temperatures; forms semicarbazone, M.P. 192.
29. B.P. 164.
30. Volatile with superheated steam.
31. B.P. 185.
32. B.P. 280. Treated with $AlCl_3$ it ring-closes to 1-indanone, *m* 42, (*Bull.soc.chim.* (4), **41**, 942 (1927)).
33. B.P. 198.5 Peculiar spicy odor.
34. Upon solidifying, the crystals grow upwards and branch out, if pure; if impure, the surface remains flat. This behavior is also true of α-hydnocarpic acid, $C_{16}H_{22}O_2$.
35. B.P. 189; v.s.
36. B.P. 265.5; *s*. Warmed with dil. H_2SO_4 and MnO_2, odor of benzaldehyde.
37. Long heating at 100 gives the anhydride, *m* 128–130.
38. Steam distillation gives the anhydride.
39. B.P. 302–304.
40. Monoanilide, *m* 164; dianilide, *m* 179. Aq. soln. by boiling yields the anhydrous acid, M.P. 153; over H_2SO_4 or at 130 likewise. Floats on CCl_4 (differentiation from tartaric acid). Warmed with acetic anhydride and pyridine it exhibits a carmine coloration.
41. Anhydrous acid melts at 189.5. When compound is treated with acetic anhydride it rapidly decomposes to CO_2 and CO.
42. B.P. 259 at 751 mm.
43. *s* but not v.s.
44. Boils above 360 with a light decomposition.
45. B.P. 263; *s;* v.s.
46. B.P. 249.
47. If pure, the B.P. is 137; ordinarily contains 3% fumaric acid and boils at 130.
48. B.P. 230–232. Gives the pyrrole test.
49. B.P. 300.
50. About 100 mg boiled in t.t. with 3 ml acetic anhydride 3 min. and diluted with 3 ml acetic acid gives a yellow-red soln. with green-yellow fluorescence (diff. from pyromucic).
51. *s*; *m* under water at 80°.
52. Warmed with acetic anhydride and pyridine gives an emerald color. So do racemic acid and *d*-tartaric acids.
53. 1 mg dissolved in 3 drops H_2SO_4 immed. gives intense orange-red coloration, soon red-violet at edges.
54. *s*; v.s. Treated with H_2SO_4 and MeOH and warmed gives the characteristic odor of oil of wintergreen (methyl salicylate).
55. Not v.s (Diff from citraconic). Anilide obtained only by boiling excess of amine with acid.
56. Melting point of anhydrous acid 182; that of hydrate (1-H_2O) given as 173 and 174.
57. *s*; v.s.
58. B.P. 275-280.
59. Ammonium salt distilled with Zn dust gives the pyrrole test.
60. M.P. may vary widely (formation of itaconic acid and CO_2). Warmed with acetic anhydride and pyridine gives a beautiful violet-red coloration (a very sensitive test).
61. *s*; v.s. Tastes faintly sweet.
62. *s*, but not v.s.
63. The mono-*p*-toluidide: *m* 150 (slowly), 160-165 (quickly heated). The monoanilide, *m* 170. The figures 201 and 253 represent the di-*p*-toluidide and dianilide, respectively.
64. *s*, but not v.s.
65. Titrated with bromothymol blue as indicator.
66. Melts at 223-224 if rapidly heated. Gives pyrrole test.
67. M.P. may vary, often 222–240*d*. Aq. soln. treated with a few drops of KCN soln. gives red color, disappearing except at surface, and reappearing on shaking.
68. Melts in sealed tube at 287.

[a] For list of abbreviations, see p. 356.

69. Ba salt (+$4H_2O$) very insoluble (diff. from isophthalic).

70. Sublimes below M.P. with formation of anhydride. Ba salt (+$6H_2O$) very soluble (diff. from terephthalic).

71. Trimethyl ester: *m* 144; triethyl ester: *m* 133.

72. On ammonolysis with concentrated ammonia gives amide, *m* 99 (87).

73. Naphthalimide *m* 300° is formed by heating compd. with excess aq. NH_3; deriv. is purified by boiling with Na_2CO_3 soln. The compd. boiled with aniline forms *N*-phenylnaphthalimide *m* 202°.

74. See also Table 42.

TABLE 5

Alcohols (Liquid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Melting Point of Derivatives (°C)		
					Recommended		Others
					α-Naphthyl-urethan	3,5-Dinitro-benzoate	Phenyl-urethan
1	Methyl			64.65	124	108*	47
2	Ethyl			78.32	79	93	52
3	Isopropyl			82.4	106	123	75
4	*tert*-Butyl		25.5	82.5	101	142	136
5	Allyl			97.1	108	49	70
6	*n*-Propyl			97.15	80	74	57
7	*sec*-Butyl			99.5	97	76	64.5
8	*tert*-Amyl			102.35	72	116	42
9	Isobutyl			108.1	104	87	86
10	3-Methyl-2-butanol (*sec*-Isoamyl)	1		114	109		68
11	3-Pentanol (Diethyl carbinol)			116.1	95	101	49
12	*n*-Butyl			118	71	64	61
13	2-Pentanol (*sec*-Amyl)	1		119.85	74.5	62	
14	Pinacolyl (3,3-Dimethyl-2-butanol)			120.4		107	78
15	2,3-Dimethyl-2-butanol			120.5	101	111	66
16	2-Methyl-2-pentanol			121		72	
17	3-Methyl-3-pentanol			123	83.5	96.5	43.5
18	2-Methoxyethanol ("Methyl cellosolve")	5		124.5	113		
19	1-Chloro-2-propanol			127			
20	2-Methyl-3-pentanol			127.5		85	50
21	(*l*)2-Methylbutanol (active Amyl)			128.9	82	70	
22	2-Chloroethanol (Ethylene chlorohydrin)			129	101		51
23	4-Methyl-2-pentanol			132	88	65	143
24	Isoamyl (3-Methylbutanol)			132	68	61	57
25	3-Methyl-2-pentanol			134.2/749mm	72	43.5	
26	2-Ethoxyethanol ("Ethyl cellosolve")	5		134.8	67	75	
27	3-Hexanol			135.5		77	
28	2,2-Dimethylbutanol			136.7	81	51	66
29	*n*-Amyl (1-Pentanol)			138*	68	46.4	46
30	2-Hexanol			139.8			
31	2,4-Dimethyl-3-pentanol	2		140			95
32	Cyclopentanol			140.85	118		132.5
33	3-Ethyl-3-pentanol	2		142			
34	3,3-Dimethylbutanol			143	118		132.5
35	2,3-Dimethylbutanol			145		51.5	29
36	1-Hydroxy-2-propanone (see Table of Ketones)			146			
37	2-Methylpentanol			148.0	76	50.5	
38	2-Ethylbutanol			148.9		51.5	
39	Ethylene bromohydrin			149*d*	86		
40	Trichloroethanol		18	150			
41	2-Methyl-5-pentanol			151.6			
42	4-Methylpentanol			152		72	48
43	3-Methylpentanol			152.4	58	38	
44	4-Heptanol (Dipropyl carbinol)			156	80	64	

TABLE 5—*Continued*
Alcohols (Liquid)

	Melting Point of Derivatives (°C)—*Continued*							
	Others (Continued)							
	p-Nitrophenylurethan	*p*-Xenylurethan	3,5-Dinitrophenylurethan	*p*-Nitrobenzoate	Hydrogen-3-nitrophthalate	Hydrogen-phthalate	Pseudo-saccharin derivative	Others
1	179.5	127	127	96	153*	82.5*	182*	
2	129	119	83	57	158*	48	219*	
3	116	138	112	110 (108)	154*		137*	
4			166*d*	116				
5	108		114	28	124			
6	110	129	97	35	145.5*	54.4*	124.5*	
7	75	105.5	120	26	131*	60	65.5*	
8				85				
9	80		119	69	180.5*	65	100*	
10					127	39		
11								
12	95.5	109	70	36	147*	73.5	96*	
13		94.5			103	61	38*	
14						86		
15								
16								
17								
18	111			51	129			
19								
20					150.7	70		
21					158			
22					98			
23		95.5		26				
24	97.5				163.3*		64*	
25								
26	80				118			
27						77		
28						69		
29	91	99	58	11.2	136*	75.5	62*	
30								
31					155 N(2A)			
32								
33								Allophanate, 152
34								
35								
36								
37		99			145 (141)			
38						54		
39								
40								
41								
42					140			
43								
44				35		60		

TABLE 5—*Continued*

Alcohols (Liquid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Melting Point of Derivatives (°C)		
					Recommended		*Others*
					α-Naphthyl-urethan	3,5-Dinitro-benzoate	Phenyl-urethan
45	Hexyl (1-Hexanol)			157.5	59	58.4	42
46	2-Heptanol			158.7	54	49.4	
47	2,4-Dimethylpentanol			159.8			
48	Cyclohexanol	7	25.2 (16)	161.1	129	113	82
49	2-Methylhexanol			165			
50	4-Methylhexanol	3		165	50		
51	2-Methylcyclohexanol (*cis* or β) (Hexahydro-*o*-cresol)	4		165.3		99	94
52	2-Ethylpentanol			166			
53	4-Hydroxy-4-methyl-2-pentanone (see Table of Ketones)			166			
54	2-Methylcyclohexanol (*trans* or α)	4		167.4	155	115	105
55	Furfuryl	6		170	130	81	45
56	2,6-Dimethyl-4-heptanol	2		172.5			62
57	3-Methylcyclohexanol (*cis* or β)			173-4		91-2	87-8
58	3-Methylcyclohexanol (*trans* or α)			174-5	122	97-8	93-4
59	4-Methylcyclohexanol (*cis* or β)			$173\text{-}4_{760mm}$		134	
60	4-Methylcyclohexanol (*trans* or α)			$173\text{-}174.5_{745mm}$	160	140	125
61	2-Butoxyethanol (Butyl "cellosolve")	5		$170\text{-}6_{743mm}$			
62	Heptyl (1-Heptanol)			176.8	59.5	46	65
63	Tetrahydrofurfuryl	6		177		83-4	61
64	2-Methyl-1,2-propanediol (Isobutylene glycol)			178			140.5
65	2-Octanol			179	62.5	32	oil
66	Cyclohexanemethanol (Hexahydrobenzyl)			182			
67	2,3-Dichloropropanol			182	93		73
68	2,3-Butanediol	8		182.5			201 (*bis*)
69	4-Methylheptanol			182.7			
70	2-Ethylhexanol			184.6	61		34
71	1,2-Propanediol (α-Propylene glycol)	9		187.4			153 (143)
72	Diethylene glycol monomethyl ether ("Methyl carbitol")	11		194			
73	5-Nonanol			194			
74	Octyl (1-Octanol)			195	66	61	74
75	2-(2-Ethoxyethoxy)-ethanol ("Carbitol"; diethylene glycol monoethyl ether)			196		oil	
76	2-Methyl-2,4-pentanediol	10		196			
77	Glycol (Ethylene glycol)			197.85	176	169	157
78	2-Nonanol			198.2	55.5	42.8*	
79	*l*-Linaloöl			199	53		66
80	α-Methylbenzyl (α-Phenylethyl)		20.1	202	106	95	92
81	Benzyl			205.5	134	113	77
82	1,3-Butanediol			207.5			122-123
83	2-Decanol			211	69	44	
84	*n*-Nonyl (1-Nonanol)	12		213.5	65.5	52	60N (69)
85	1,3-Propanediol (Trimethylene glycol)			214.7	164	178	137

TABLE 5—*Continued*

Alcohols (Liquid)

	MELTING POINT OF DERIVATIVES (°C)—*Continued*							
	Others (Continued)							
	p-Nitrophenylurethan	*p*-Xenylurethan	3,5-Dinitrophenylurethan	*p*-Nitrobenzoate	Hydrogen-3-nitrophthalate	Hydrogenphthalate	Pseudosaccharin derivative	Others
45	104	98	75	6.7	124*	25	60*	
46						57.5		
47		75			155			
48		166		50	160	99		
49		88.5			132			
50					144			
51				56		105		
52		77.5			128			
53								
54				65		125		
55				76		85		
56				118				
57				65		82-3		
58				58		93-4		
59				94		119		
60				67		120		
61	59				120.5			
62	105		61		127*	17.5	55*	
63				46-8				
64								
65	oil			28		55		
66								
67								
68								
69					133		34*	
70		80			108		53.5*	
71								
72	73.5 (66)				92 (87-90)			
73						45		Allophanate, 158
74	111		69	12	128*	22	46*	
75	66			oil	oil			
76								
77	135.5			140				
78						42-44		
79				70				
80				43		108		
81	157	156	181	85	176	106	130*	
82								
83						69		
84			66		125*	42.5	49*	
85				119				

TABLE 5—*Continued*

Alcohols (Liquid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Melting Point of Derivatives (°C)		
					Recommended		*Others*
					α-Naphthyl-urethan	3,5-Dinitro-benzoate	Phenyl-urethan
86	α,α-Dimethylphenethyl (Benzyldimethylcarbinol)	13	24	216			
87	*m*-Methylbenzyl (*m*-Tolylcarbinol)			217	116		
88	*p*,α-Dimethylbenzyl (Methyl-*p*-tolylcarbinol)			219			96
89	2,3-Dibromo-2-propanol			219*d*			84
90	α-Ethylbenzyl (α-Phenylpropyl)			219	102		
91	Phenethyl (β-Phenylethyl)			219.8	119	108	78
92	α-Terpineol (*m* 35; v.s.)	14		221	152	79	113
93	Citronellol	15		222			
94	α-Isopropylbenzyl (Isopropylphenyl-carbinol)	16		222-4	116-7		
95	2-Hendecanol			228-9			
96	Geraniol			230	48	63	
97	1,4-Butanediol (Tetramethylene glycol)		19.5	230 (235)	199 (*bis*)		183.5* (*bis*)
98	Decyl (1-Decanol)			231	73	56 7	60
99	Glycol monophenyl ether	17		237 (245)			
100	3-Phenylpropanol			237.4		92	45 (48)
101	Pentamethylene glycol			238	147		174
102	Diethylene glycol (β,β′-dihydroxydiethyl ether)	18		244.5	149	151*	
103	*o*-Methoxybenzyl			247	136		
104	Triethylene glycol	19		285			
105	Glycerol	20	17.9	290	192 (tri)		180 (tri)
106	*p*-Anisyl-methylmethanol	21A		310*d*			83
107	Oleyl (*cis* 9-Octadecenol)	21B	0	335	45N		
108	Undecanol (Hendecyl; *n*-undecyl)		15.85			55	52
109	α-Propylbenzyl		16		99		

TABLE 5—*Continued*

Alcohols (Liquid)

	Melting Point of Derivatives (°C)—*Continued*							
	Others (Continued)							
	p-Nitrophenylurethan	*p*-Xenylurethan	3,5-Dinitrophenylurethan	*p*-Nitrobenzoate	Hydrogen-3-nitrophthalate	Hydrogenphthalate	Pseudosaccharin derivative	Others
86								
87								
88								
89								
90			71					
91	135		139	62*	123	189		
92				139		118		
93								
94								
95						50		
96				35	117	47		Allophanate, 124.5
97				175 (di)				Dibenzoate, 81-2
98	117		70	30.2 (29.8)	122.8*	38*	47.5*	
99					113			
100	104			47	117			
101								
102								
103								Allophanate, 180
104								Benzoate, 59
105	216			188 (tri)				(see Note)
106								
107	85-91							Allophanate, 135 and 129 (isomers)
108	99.5		62		123.3*	44	58.5*	
109				58		91		

TABLE 6

Alcohols (Solid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Melting Point of Derivatives (°C) — *Recommended* α-Naphthyl-urethan	*Recommended* 3,5-Dinitro-benzoate	*Others* Phenyl-urethan
1	Dodecyl (lauryl)		23.9	259	80	60	74
2	*p*-Anisyl		25	258			92
3	*m*-Nitrobenzyl (see Table on Nitro Compounds)		27				
	Diethanolamine (see Table of Amines)		28				
4	Tridecanol		30.63				
5	Cinnamyl		33	257	114	121	90-91.5
6	Elaidyl (*trans* 9-Octadecenol)	21B	34	333	71N		56-57
7	*o*-Methylbenzyl (*o*-Tolycarbinol)		35	v.s.			79*
8	α-Terpineol		35	221	152	79	113
9	Tetradecanol (Myristyl)		37.7				71
10	Fenchyl		38-39	201.5	149	104	
11	Pinacol (hydrate, *m* 46°) (Tetramethylethylene glycol)	22	43	173	215		
12	*l*-Menthol	23	43	216	126 (119)	153	112
13	Pentadecanol		(α) 44 (β) 39		(α) 72		
14	Cetyl (Hexadecanol)		50		82	66	73
15	2,2-Dimethylpropanol (Neopentyl)		52	113	100		144
16	Piperonyl		52 (58)				102
17	*p*-Methylbenzohydrol (Phenyl-*p*-tolyl carbinol)		53				
18	Heptadecanol		(α) 54 (β) 45.7	310			
19	Octadecanol (Stearyl)		58				80
20	*p*-Methylbenzyl (*p*-Tolylcarbinol)		59	217 v.s.			79
21	Nonadecanol		62				
22	4-Methoxybenzohydrol		60				
23	Eicosanol		65 (68)				76
24	Methyl-α-naphthyl carbinol		66				
25	1,2-Diphenylethanol		67				
26	Benzohydrol (Diphenylmethanol)	24	68	288	139 (136)	141	140
27	*o*-Nitrobenzyl (see Table of Nitro Compounds)		74				
28	Myricyl		85				96
29	*o*-Hydroxybenzyl (see Table of Phenols)		86-87				
30	Phenacyl (see Table of Ketones)		86				
31	*p*-Nitrobenzyl (see Table of Nitro Compounds)		93				
32	Benzoin (see also under Table of Ketones)		133	344	140		165
33	Cholesterol (anhydrous)		148.5		176		
34	Triphenylmethanol (Triphenylcarbinol)		162	380			
35	Ergosterol (anhydrous)		165		202		
36	*d*-Mannitol		166				303
37	*d*-Borneol	25	205	212	127	154	138

TABLE 6—*Continued*

Alcohols (Solid)

	Melting Point of Derivatives (°C)—*Continued*							
	Others (Continued)							
	p-Nitrophenyl urethan	*p*-Xenylurethan	3,5-Dinitrophenyl urethan	*p*-Nitrobenzoate	Hydrogen-3-nitrophthalate	Hydrogen-phthalate	Pseudo-saccharin derivative	Others
1	117		81	45 (41.9*)	124*	50.3*	54*	
2								
3								
4				37.4*	124-124.2*	52.4-52.7	66*	
5				78				
6								
7								
8				139		118		
9				51.2*	123.5*	60*	62*	
10				109	95	169		
11								
12				62		110N		
13				45.8*	122.5*	60.5	72*	
14	118		86	58.4* (52)	122*	67	69.5*	
15						71		
16								oxdn →
17								Ketone *m* 60
18				53.8*	121.5*	66.5*	76*	
19	115		88	64.3*	119*	72.5*	74.5*	
20								
21				58.9*				
22								
23				69.4*				
24						132		
25						131*		
26				132		165		
27								
28								
29								
30								
31								
32	183		220*d*	123				
33	205		198	185 (190-3)		161		See Table 42
34								
35								
36								
37				153		165		

1. The M.P. of derivatives are for the *dl*-form of the alcohol; for example, the hydrogen phthalate of the *d*- or *l*- form melts at 34.

2. Camphor-like odor.

2A. Cf. C.A. **37**, 4686[3] (1943).

3. Odor of amyl alcohol.

4. The hexahydro-*o*-cresol obtained from *o*-cresol consists of a mixture of two stereoisomers, each of which can be resolved into two optically active forms. The derivatives listed are for the *dl*-, *cis*- or *β*- form; likewise those listed for the *trans*-isomer (*m* 167.4) are for the *dl*-form.

5. The lower monoalkyl ethers of ethylene glycol are commonly known as "cellosolves." The esters resulting from the reaction of the hydroxyl group are as a rule liquids, and unsuitable for derivatives.

6. Furfuryl alcohol instantly reduces permanganate in cold and decolorizes bromine water, whereas tetrahydrofurfuryl does not.

7. Camphor-like odor. Oxidation with chromic acid gives cyclohexanone; with nitric acid, gives adipic acid.

8. The derivative listed is that of the *meso*-form; other derivatives thereof are the dibenzoate, *m* 76, and the di-*p*-bromobenzoate, *m* 139.5. The commercial product obtained by fermentation is a mixture of the *meso*- and *dl*- forms.

9. Viscous liquid; tastes sweet. A few drops distilled with anhyd. $ZnCl_2$ gives propionaldehyde.

10. Odor of pinacol.

11. The 3-nitrophthalate monohydrate melts at 87–90, and the anhydrous at 91.4–92.2.

12. Other values for the M.P. of the phenylurethan are 69, 62–4.

13. This compound heated with equal volume of acetic anhydride and a few drops of H_2SO_4, diluted and extracted with ether, gives dimethylstyrene (*b* 180–2).

14. Lilac-like odor. Shaken with HI gives dipentene salt; similarly with dry HCl gas gives a mass of crystals of the hydrochloride (*m* 50).

15. Rose-like odor. Isomeric with Rhodinol (2,6-dimethyl-2-octene-8-ol). Oxidation gives *β*-Methyl-adipic acid (*m* 89).

16. With chromic oxide and sulfuric acid mixture this alcohol is oxidized to isopropylphenyl ketone (see Table of Ketones).

17. Benzoate, *m* 64; *p*-toluenesulfonate, *m* 80.

18. Somewhat viscous and slightly sweet.

19. A derivative may be obtained by reaction with triphenylchloromethane (see Bibliography). M.P. of *bis*- (triphenylmethyl ether) 142.

20. Tribenzoate (see Chapter 10) 71–2, also 75–6; tri-*p*-toluenesulfonate, *m* 103.

21A. Odor of anise. Oxidation yields *p*-Methoxyacetophenone, *m* 38.

21B. Oleyl (*cis*) is isomeric with elaidyl (*trans*); see Table 6, compd. 6. Heated at 95° for 2 hrs. in AcOH and perhydrol → 9,10-dihydroxyoctadecanol melting at 82° if compd. is oleyl and at 125° if compd. is elaidyl (*J. Chem. Soc.*, **1933**, 247). The derivative listed as *α*-naphthylurethan is *β*-naphthylurethan (*Compt. rend.*, **185**, 281).

22. Pinacol hydrate over NaOH loses water after several days, forming eventually the anhydrous compound. When boiled with dilute H_2SO_4 it gives pinacolone, having a strong peppermint odor; heated with B_2O_3, gives a good yield of pinacolone.

23. Strong peppermint odor. The hydrogen phthalate derivative (*m* 110) slowly changes in contact with the mother liquor to the stable form, *m* 122.

24. Easily oxidized by chromic acid mixture to benzophenone.

25. Strong camphor odor. Shaken with 50% HNO_3 for 3 hrs. and then diluted, gives *d*-camphor, *m* 179.

TABLE 7
Phenols (Liquid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Melting Point of Derivatives (°C)			
					Recommended		Others	
					α-Naphthylurethan	3,5-Dinitrobenzoate	*N*-Phenylurethan	*N*-*p*-Nitrophenylurethan
1	*o*-Chlorophenol		7	175	120			
2	*o*-Bromophenol		5	195	129			
3	Salicylaldehyde (see Tables of Aldehydes)			197				
4	*m*-Cresol		12	203	128	165.4*	125 (122)	
5	Guaiacol		28	205 v.s.	118	141.2*	136	
6	*o*-Ethylphenol			207		108	141	
7	2,4-Dimethylphenol		27	211.5*	135	164.6*	112	
8	*m*-Chlorophenol		28 (33)	214	158			
9	*m*-Ethylphenol		−4	217			140	
10	*o*-Ethoxyphenol		28	217				
11	*o*-Hydroxyacetophenone		28	218				
12	Methyl salicylate	1		224				
13	Ethyl salicylate	2		234				
14	*p*-Isobutylphenol			235.9*				
15	Carvacrol		1	237.5	116	83	135 (140)	
16	*m*-Methoxyphenol		−17.5	244	129			
17	*p*-Butylphenol		22	248			115	
18	*p*-Amylphenol		23	248-253				
19	Eugenol		−9.1	253	122	130.8*	95	
20	Isoeugenol			267.5	150	158.4*	118 (*cis*) 152 (*trans*)	

TABLE 8
Phenols (Solid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Melting Point of Derivatives (°C)			
					Recommended		Others	
					α-Naphthylurethan	3,5-Dinitrobenzoate	*N*-Phenylurethan	*N*-*p*-Nitrophenylurethan
1	*o*-Cresol		31	191	142	138.4*	141	
2	*p*-Cresol		36	202	146	188.6*	115	
3	2,4-Dibromophenol		36					
4	*p*-Chlorophenol		37	217	166			
5	Phenyl salicylate (Salol)	3	42				112N (242)	
6	Phenol		42	183	133	145.8*	126	161
7	2,4-Dichlorophenol		43	209				
8	*o*-Nitrophenol	4	45	v.s.	113			
9	*p*-Ethylphenol		47	219	128	133	120	
10	2,6-Dimethylphenol		49		176.5	158.8*	133	
11	Thymol		51.5	233.5	160	103.2	107	
12	4-Chloro-*m*-Cresol (2-Chloro-5-hydroxy-toluene)		52		154			
13	*p*-Methoxyphenol (Hydroquinone methyl ether)		56	244				
14	Orcinol (hyd.)	5	56-58					
15	3,4-Dimethylphenol		62.5	225	142	181.6*	120	

TABLE 7—*Continued*
Phenols (Liquid)

	Melting Point of Derivatives (°C)—*Continued*								
	Others (Continued)								
	p-Xenyl-urethan	*N,N*-Diphenyl-urethan	*p*-Nitro-benzoate	(Mono, di, and tri) benzoate	(Mono, di, tri) acetate	(Mono, di, tri) bromo-derivative	Aryloxy-acetic acid	*p*-Toluene sulfonate	2,4-Dinitro-phenyl ether
1							145		99
2						95	143		89
3									
4	164	101	90	55		84(tri)	103	51	74
5			93	57		116(tri)	121		97
6			57	39			141		
7	184		105	38			141		
8							110		75
9			68	52			77		
10				31					
11									
12									
13									
14							125		
15	166		51			46	151		
16						104(tri)	118		
17			68	27			81		
18				51.5			90		
19		108	81	70	30	118(tetra)	81 and 100		115
20			109		80		94 and 116		130

TABLE 8—*Continued*
Phenols (Solid)

	Melting Point of Derivatives (°C)—*Continued*								
	Others (Continued)								
	p-Xenyl-urethan	*N,N*-Diphenyl-urethan	*p*-Nitro-benzoate	(Mono, di, and tri) benzoate	(Mono, di, and tri) acetate	(Mono, di, and tri) bromo-derivative	Aryloxy-acetic acid	*p*-Toluene sulfonate	2,4-Dinitro-phenyl ether
1	151	73	94			56(di)			90
2	198	94	98	70		108(tetra)	135	70	93
3				97		95(tri)			135
4				93			156		126
5			111	81	99.5				
6	173	105	127	69		95(tri)	89(99)	96	69
7				97		68	138		119
8				142		117	158		142
9			81	60			97		
10	198					79	139.5		
11	194		70	33		55	149	71	67
12				86					
13				87	32		110-112		
14									
15	183			58.5		171(tri)	162.5		

TABLE 8—*Continued*

Phenols (Solid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Melting Point of Derivatives (°C)			
					Recommended		*Others*	
					α-Naphthylurethan	3,5-Dinitrobenzoate	*N*-Phenylurethan	*N*-*p*-Nitrophenylurethan
16	*p*-Bromophenol	6	64		169			
17	4-Homopyrocatechol		65	252			166	
18	2,4,6-Trichlorophenol		68					
19	*o*-Phenylphenol		67.5*	275				
20	3,5-Dimethylphenol		68 (64)	220 v.s		195.4*	148	
21	Mesitol		70	220			142	
22	Pseudocumenol (2,4,5-Trimethylphenol)		71	232			110	
23	2,5-Dimethylphenol		74.5	212	173	137.2*	161	
24	8-Hydroxyquinoline (see Tables of Tertiary Amines)		75					
25	*m*-Phenylphenol (3-Hydroxydiphenyl)		78	300				
26	Isodurenol (2,3,4,6-Tetramethylphenol)		79-81	230-250			179	
27	3,5-Dinitro-*o*-cresol		86.5					
28	Saligenin (*o*-Hydroxybenzyl alcohol)		86-87					
29	*p*-*tert*-Amylphenol		93	260-5				
30	1-Naphthol (α-Naphthol)		94	280	152	217.4*	178	
31	*p*-Iodophenol		94					
32	2,4,6-Tribromophenol		95		153			
33	2-Naphthyl salicylate	7	95.5					
34	*m*-Nitrophenol		97		167			
35	*p*-*tert*-Butylphenol		100	237				
36	*m*-Hydroxybenzaldehyde (see Tables of Aldehydes)		104					
37	Pyrocatechol (Catechol)		105	245 (240)		152	169	
38	1,2-Naphthalenediol		108					
39	Orcinol		108		160	190	154	
40	2,4,6-Trinitro-*m*-cresol	8	109					
41	*o*,*o*′-Biphenol (2,2′-Dihydroxybiphenyl)		110	326			145	
42	Resorcinol		110	280.8*		201	164	232
43	Bromohydroquinone		110					
44	*p*-Nitrophenol	4	114		151			
45	2,4-Dinitrophenol	9	114					
46	Ethyl *p*-hydroxybenzoate		115					
47	*p*-Hydroxybenzaldehyde (see Tables of Aldehydes)		116-7					
48	Trinitrophenol (Picric acid)	10	122.5					
49	2-Naphthol (β-Naphthol)		123	286	157	210.2*	156	
50	2,6-Dichloro-4-nitrophenol		125*d*					
51	Methyl *p*-hydroxybenzoate		131					
52	*p*-Cyclohexylphenol		132			168*		
53	Pyrogallol		133				173(tri)	
54	*p*-Hydroxybenzophenone (see also Ketones)		135					
55	2,4-Dinitronaphthol		138					

TABLE 8—*Continued*

Phenols (Solid)

	Melting Point of Derivatives (°C)—*Continued*								
	Others (*Continued*)								
	p-Xenyl-urethan	*N*,*N*-Diphenyl-urethan	*p*-Nitro-benzoate	(Mono, di, and tri) benzoate	(Mono, di, and tri) acetate	(Mono, di, and tri) bromo-derivative	Aryloxy-acetic acid	*p*-Toluene sulfonate	2,4-Dinitro-phenyl ether
16				102		95(tri)	160		141
17	193			58			58(di)		
18				70					136
19				76	63			65	
20	150			24			111 (81)	83	
21				62		158(di)	139 5		
22	196			63	34.5	35	132		
23	162		87	61		178(tri)	118		
24									
25				60-61 (57-58)					
26				72					
27				135	96				
28				51(di)			120		
29				61				55	
30	190		143	56	49	105(2,4-di)	193 5	89	128
31				119			156		156
32					82	120(tetra)			135
33									
34				95		91(di)	156		138
35				82		50	86		
36									
37			169	84(di)	65(di)	193(tetra)			
38							104-106(di)		
39	196		214	88(di)	25(di)	104(tri)			
40					135				
41									
42	dec.	130	182 (175)	117		112(4,6-di)		81(di)	194
43					72(di)	186(di)			
44					81	142(2,6-di)	187		120
45				132	72	118(6-Br)			
46				94					
47									
48					76				
49		141	169	107	72	94	154	125	95
50									Methyl ether, 98 Ethyl ether, 35
51				135	85				
52			137	118.5	35				
53		212	230	90(tri)	173(tri)	158(di)			
54				115	81				
55				174					

TABLE 8—*Continued*

Phenols (Solid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Melting Point of Derivatives (°C): Recommended: α Naphthyl-urethan	Recommended: 3,5-Dinitro-benzoate	Others: *N*-Phenyl urethan	Others: *N*-*p*-Nitro-phenyl urethan
56	2-Amino-4-nitrophenol		142					
57	1,8-Naphthalenediol		142					
58	3-Nitrosalicylic (acid) (see Tables of Acids)		144					
59	2,4-Dinitroresorcinol		147					
60	Salicylic (acid) (see Tables of Acids)		158					
61	*p*-Phenylphenol (4-Hydroxybiphenyl)		165	305-8				
62	Picramic acid (see Table 42)		169					
63	Hydroquinone		171	286		317	224 (di)	
64	3,5-Dinitrosalicylic (acid) (see Tables of Acids [hydrate])		174					
65	*o*-Aminophenol (see Tables of Amines)		174					
66	1,4-Naphthalenediol		176} 192}					
67	*p*-Aminophenol (see Tables of Amines)		184					
68	2,4,6-Trinitroresorcinol (Styphnic acid)		179					
69	2,7-Naphthalenediol		186					
70	*m*-Hydroxybenzoic (acid) (see Tables of Acids)		200					
71	2-Hydroxyquinoline (see Tables of Amines)		199					
72	*p*-Hydroxybenzoic (acid) (see Tables of Acids)		210					
73	2,4-Dihydroxybenzoic (acid) (see Tables of Acids)		213					
74	Phloroglucinol		218			162	191 (tri)	
75	5-Nitrosalicylic (acid) (see Tables of Acids)		227					
76	1,5-Naphthalenediol		258} 265}					
77	Phenolphthalein		265-6* (261)				135	
78	*p*,*p*′-Biphenol (4,4′-Dihydroxybiphenyl)		275					

Notes on Phenols

1. Shaken with cold alkaline solution of $(CH_3CO)_2O$ gives a derivative, M.P. 52. Nitrated with fuming HNO_3 and H_2SO_4 at 0° gives methyl 3,5-dinitrosalicylate, M.P. 126–7.

2. Nitrated with fuming HNO_3 and H_2SO_4 gives ethyl 3,5-dinitrosalicylate, M.P. 92–3.

3. Compd. crystallizes in three modifications: (a) *m* at 42°; (b) *m* at 38.8°; (c) *m* at 28.5° (*Z. Physik. Chem.*, **29**, 71). For the m.p. of the phenylurethan see *Ber.* **40**, 1834, and C.A. **26**, 5556.

4. Nitration with fuming HNO_3 (and conc. H_2SO_4) gives picric acid, M.P. 122. *p*-Nitrophenol can be readily derivitized by reduction (see page 170)

5. See orcinol (anhydrous) M.P. 106.5–108.

6. Nitration by means of fuming HNO_3 in acetic acid yields dinitro derivative, M.P. 76.

7. Refluxed with equivalent amounts of $(CH_3CO)_2O$ and fused CH_3COONa for four hours gives a derivative, M.P. 136.

8. Methyl ether, M.P. 94.

9. Nitration with fuming HNO_3 and H_2SO_4 gives picric acid, M.P. 122.

10. Slowly heated sublimes; quickly heated explodes; addition compounds with naphthalene, M.P. 149(151); nitron picrate, M.P. 210, detects 1 : 250,000 (Bush, *Ber.* **38**, 4056).

TABLE 8—*Continued*
Phenols (Solid)

	Melting Point of Derivatives (°C)—*Continued*								
	Others (Continued)								
	p-Xenyl-urethan	*N*,*N*-diphenyl-urethan	*p*-Nitro-benzoate	(Mono, di, and tri) benzoate	(Mono, di, and tri) acetate	(Mono, di, and tri) bromo-derivative	Aryloxy-acetic acid	*p*Toluene sulfonate	2,4-Dinitro-phenyl ether
56				*d*> 200				122	
57					142				
58									
59							155	126-7	
60									
61				150	88			179	118
62									
63			258	204(di)	123	186(di)		159(di)	
64				163(mono)					
65									
66				169(di)	128-30(di)				
67									
68									Dimethyl ether, 125
69		176		139(di)	172(di)				
70									
71									
72									
73									
74			283	174(tri)	105(tri)	151(tri)			
75									
76				235(di)	160(di)				
77				169(di)	143				
78				241(di)	161 (164)				

TABLE 9

Esters (Liquid)[a]

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density[b]	Refractive Index
1	Ethyl nitrite			17	$0.900D_4^{15}$	
2	Methyl formate		−99	31.5	0.97421	$1.34648 = n^{15}_{He(yel.)}$
3	Ethyl formate		−79.4	54.2	0.92247	1.35975
4	Methyl acetate			57.1	0.9274	1.36170
5	Methyl nitrate			65	$1.217D_4^{15}$	
6	Butyl nitrite			75	0.911	
7	Ethyl acetate		−83.6	77.15	0.90055	$1.37005 = n_D^{25}$
8	Methyl propionate		−87.5	79.9	0.9151	1.3779
9	Methyl acrylate	1		80.3	0.961	1.3984
10	*n*-Propyl formate			81	0.918	
11	Ethyl nitrate			87	$1.130D_4^4$	
12	Isopropyl acetate		−73.4	88.9	$0.9166D_4^{25}$	$1.3740 = n_D^{25}$
13	Dimethyl carbonate			90.5	1.0694	1.3687
14	Methyl isobutyrate		−84.7	92.6	0.8906	1.3840
15	Ethyl chloroformate			93	$1.144D_4^{15}$	
16	*tert*-Butyl acetate			97.8	$0.8620D_4^{26}$	$1.3840 = n_D^{26}$
17	Isoamyl nitrite			99	$0.880D_4^{15}$	
18	Ethyl propionate		−73.9	99.1	0.8889	1.3853
19	Methyl methacrylate	1		99		
20	Ethyl acrylate	1		101	0.9136	1.4059
21	Methyl trimethylacetate (Pivalate)			101	$0.891D_4^0$	1.4228
22	*n*-Propyl acetate			101.6	0.8834	1.38468
23	Methyl butyrate			102.3	0.8982	1.3879
24	Allyl acetate			104	0.9276	1.40488
25	Trimethyl orthoformate			105	0.9676	1.3793
26	*n*-Butyl formate		−91.9	106.6	0.8885	1.38940
27	*n*-Propyl nitrate			110	1.063	
28	Ethyl isobutyrate		−88.2	111.0	0.86930	1.3903
29	*sec*-Butyl acetate			112.0	0.8648	1.3865
30	Methyl isovalerate			116.7	0.8808	1.3900
31	Isobutyl acetate			117.2	0.8747	1.39008
32	Ethyl butyrate		−100.8	121.6	0.87917	$1.39475 = n_{He}^{15}$
33	*n*-Butyl acetate			126.1	$0.87636D_4^{25}$	$1.39614 = n_D^{15}$
34	Diethyl carbonate		−43.0	126.8	0.9752	1.3852
35	Methyl valerate		−91.0	127.7	0.885	$1.3993 = n_D^{15}$
36	Methyl (mono) chloroacetate			130 (132)	1.238	
37	Ethyl isovalerate		−99.3	134.7	0.86565	1.4009
38	*n*-Butyl nitrate			136	1.048	
39	Methyl pyruvate	2		137	1.154	
40	Isobutyl propionate		−71.4	137	$0.8876D_4^0$	1.3975
41	Ethyl crotonate			138	0.91752	1.42524
42	Isoamyl acetate			142	0.8674	1.40034
43	Ethylene glycol monomethyl ether acetate ("Methyl Cellosolve acetate")			144	$1.0067D_{20}^{20}$	
44	*n*-Butyl propionate			144	0.895	
45	Methyl lactate (*dl*)			144.8	1.0931	1.4144
46	Ethyl (mono) chloroacetate			145	1.158	
47	β-Chloroethyl acetate			145	1.178	
48	Triethyl orthoformate			145.5	0.8909	1.3922
49	Ethyl valerate		−91.2	145.5	0.8739	1.40094
50	Ethyl α-chloropropionate			146	1.087	
51	*n*-Amyl acetate		−70.8	148.8	0.8756	1.4031
52	Methyl caproate		−71.0	151.2	0.88464	$1.40699 = n^{15}_{He(yel.)}$
53	Ethyl lactate			154.5	1.030	1.410
54	Ethyl pyruvate	3		155	$1.0594D_4^{15.6}$	$1.408 = n_D^{15.6}$

[a] Many esters not listed in this Table may be found as "derivatives" in the tables for Acids and Alcohols; sulfonate and sulfinate esters are not included and for references on these consult Bibliography section.
[b] Density is given at 20°/4° unless otherwise indicated.

TABLE 9—*Continued*

Esters (Liquid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density	Refractive Index
55	Ethylene glycol monoethyl ether acetate ("Cellosolve acetate")			156	$0.9749D_{20}^{20}$	
56	Isobutyl butyrate			157	0.8620	1.402
57	Ethyl (mono) bromoacetate			159	1.506	
58	Ethyl glycolate			160	$1.0869D_4^{15}$	
59	Isoamyl propionate			160	0.870 (0.858)	
60	Ethyl α-bromopropionate			162	1.329	
61	Tetraethyl silicate	4		165.5 (168.5)	0.93975	1.38619
62	Ethyl caproate		−67.5	167.9	0.8710	1.40727
63	Ethyl trichloroacetate			168	$1.369D_4^{16}$	
64	Methyl acetoacetate			170	$1.0765D_4^0$	1.41964
65	Methyl enanthate (Heptoate)		−55.8	173.8	0.88011	$1.41334 = n^{15}_{He(yel.)}$
66	Cyclohexyl acetate			175	$0.9854D_4^0$	
67	Furfuryl acetate			176	$1.1175D_{20}^{20}$	
68	Ethyl β-bromopropionate			179	1.425	
69	Ethyl acetoacetate			181	1.025	1.41976
70	Methyl furoate (Pyromucate)			181.3	1.180	
71	Dimethyl malonate			181.5	1.1539	1.41398
72	*n*-Amyl-*n*-butyrate			185.0	$0.8713D_0^0$	
73	Diethyl oxalate			186	1.0785	1.41043
74	Methyl sulfate	5		188		
75	Ethyl enanthate (Heptoate)		−66.3	188.6	0.86856	$1.41537 = n^{15}_{He(yel.)}$
76	Ethylene glycol diacetate		−31	190.2	1.1040	1.4150
77	Heptyl acetate		−50.2	192.5	$0.87070D_4^{15}$	$1.41653 = n^{15}_{He(yel.)}$
78	Methyl caprylate		−41	194.6	$0.8942D_0^0$	$1.4069 = n_D^{45}$
79	Dimethyl succinate		18.2	196.0	1.1192	1.41965
80	Ethyl methylmalonate			196	$1.019D_4^{15}$	
81	Phenyl acetate			196.7	$1.0809D_{15}^{15}$	1.503
82	Diethyl malonate		−51.5	199.3	1.05513	1.41618
83	Methyl benzoate		−12.5	199.6	$1.0937D_4^{15}$	1.5164
84	Benzyl formate			203	1.080	1.51537
85	Ethyl levulinate	6		205.8	1.01114	1.42288
86	γ-Butyrolactone			206		
87	γ-Valerolactone			207		
88	*n*-Amyl valerate			207.4	$0.8825D_4^0$	$1.4181 = n_D^{15}$
89	*o*-Tolyl acetate (*o*-Cresyl acetate)			208	1.048 (1.045)	
90	Ethyl sulfate	7		208	1.1842	
91	*n*-Propyl *n*-heptylate			208	0.86556	
92	Ethyl caprylate		−43.1	208.5	0.8667	1.41775
93	Trimethylene glycol diacetate			210	1.070	
94	*m*-Tolyl acetate (*m*-Cresyl acetate)		12	212	1.049	1.4978
95	*p*-Tolyl acetate (*p*-Cresyl acetate)			212.5	1.053 (1.050)	1.500
96	Ethyl benzoate		−34.2	213.2	1.0465	1.506
97	Methyl pelargonate			214	$1.0384D_0^0$	
98	Methyl *o*-toluate			215	$1.0731D_4^{15}$	
99	Benzyl acetate			217.0	1.055	1.5200
100	Diethyl succinate		−21	217.7	1.0398	1.41975
101	Diethylene glycol monoethyl ether acetate ("Carbitol acetate")			218	$1.0114D_{20}^{20}$	
102	Diethyl fumarate		+0.2	218.4	$1.05721D_4^{15}$	1.44103
103	Methyl phenyl acetate			220	$1.0633D_{16}^{16}$	$1.5091 = n_D^{16}$
104	*l*-Linalyl acetate			220	0.8951	1.4460
105	Methyl *m*-toluate			221	$1.068D_4^{15}$	

TABLE 9—*Continued*

Esters (Liquid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density[b]	Refractive Index
106	Diethyl maleate		−17	222.7	1.07279D_4^{15}	1.44156
107	Methyl salicylate			224	1.184	
108	Methyl caprate			226		1.4161 = n_D^{45}
109	*d*-Bornyl acetate		29	226	0.991D_4^{16}	1.4633
110	Ethyl pelargonate		−36.7	227.0	0.8657	1.42200
111	Ethyl phenylacetate			227.5	1.0333	1.500
112	Ethyl salicylate			234	1.1396	1.52542
113	Ethyl bromomalonate			235	1.426D_{15}^{15}	
114	Diethyl glutarate		−24.1	237	1.02229	1.42395
115	Dimethyl *l*-malate			242	1.2334	
116	Geranyl acetate			242	0.9174D_4^{16}	1.4660
117	Thymyl acetate			245	1.009	
118	Diethyl adipate		−21	245	1.0090	1.42765
119	Ethyl caprate		−20	245	0.8650	1.42575
120	Diethylene glycol monobutyl ether acetate			246	0.9871D_{20}^{20}	
121	Diethyl *l*-malate		−10.18	253	1.1290	1.4362
122	Ethyl mandelate (*dl*)		28.1	254		
123	Diethyl pimelate		−23.8	255	0.9929	1.42985
124	Glyceryl triacetate			258	1.161D_4^{15}	
125	Methyl laurate			268	0.870	
126	Ethyl laurate		−1.7	269	0.865D_{19}^{19}	1.4321
127	Ethyl anisate		+7	269	1.1038	1.5254
128	Ethyl cinnamate		+6.5	271	1.0490	1.55982
129	Resorcinol diacetate			278	1.179	
130	Diethyl *d*-tartrate		+18.6	280	1.2028	1.44677
131	Diethyl suberate			282	0.9807	1.43236
132	Dimethyl phthalate			283.8	1.188D_{25}^{25}	1.5138
133	Diethyl azelate		−18.5	291	0.97294	1.43509
134	Triethyl citrate			294	1.1369	1.44554
135	Ethyl myristate		+11.9	295	0.861D_4^{20}	1.4362
136	Diethyl phthalate			298	1.1175	1.5019
137	Ethyl benzylmalonate			300	1.077D_4^{15}	
138	Diethyl sebacate		+1.3	307	0.9631	1.43657
139	Glyceryl tributyrate			318	1.033D_4^{17}	
140	Methyl myristate		18.5	323		1.428
141	Benzyl benzoate		+21	324*	1.1224	
142	Dibutyl phthalate			340.7	1.047D_{20}^{20}	1.4900
143	Tricresyl phosphate		−30	400 dec (275$_{80/20mm}$)	1.197D_4^{20}	1.5568

TABLE 10[a]

Esters (Solid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density	Refractive Index
1	Ethyl palmitate		24			
2	Methyl palmitate		30			1.4317
3	Ethyl stearate		33			
4	Ethyl furoate (pyromucate)		34	197	1.1175	1.4797
5	Methyl cinnamate		36	261		
6	Methyl sebacate		38	288*d*		
7	Methyl stearate		38.8			1.4346 = n_D^{15}
8	Phenyl salicylate (see also under Table of Phenols)		42			

[a] Many esters not listed in this Table may be found as "derivatives" in the tables for Acids and Alcohols; sulfonate and sulfinate esters are not included and for references on these consult Bibliography section.

TABLE 10—*Continued*

Esters (Solid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density	Refractive Index
9	Cinnamyl cinnamate		44			
10	Ethyl *m*-nitrobenzoate		47	296		
11	Dimethyl *d*-tartrate	8	48	280		
			50			
			61.5			
12	α-Naphthyl acetate		49			
13	Triphenyl phosphate	11	49	260/20mm	1.185 (liq.)	
14	Phenyl stearate		52			
15	Methyl mandelate (*dl*)		53.3	250		
16	Dimethyl oxalate	9	54	163 5/282mm		
17	Ethyl *p*-nitrobenzoate		56			
18	Dimethyl *d*-tartrate	8	48	280		
			50			
			61.5			
19	Ethyl trichloroacetate	10	66	162	1.383	1.4568
20	Phenyl benzoate		69	314		
21	2-Naphthyl acetate		71			
22	Glyceryl tristearate		71			
23	Glyceryl tribenzoate		72			
24	Trimethyl citrate		76			
25	Methyl *m*-nitrobenzoate		78			
26	Diphenyl carbonate		78	306		
27	Methyl *o*-benzoylbenzoate		80			
28	Diguaiacyl carbonate		87			
29	Dimethyl *dl*-tartrate		90	282*		
			(84*s*)			
30	Ethyl 3,5-dinitrobenzoate		94			
			(91)			
31	2-Naphthyl salicylate (see also under Table of Phenols)		95.5			
32	Methyl *p*-nitrobenzoate		96			
33	Phloroglucinol triacetate		105-106			
34	Diphenyl adipate		106			
35	2-Naphthyl benzoate		107			
36	Methyl 3,5-dinitrobenzoate		108			
37	Diphenyl succinate		121	330		
38	Hydroquinone diacetate		124			
39	Methyl terephthalate		141			
40	Pyrogallol triacetate		172			

Notes on Esters

1. Methyl acrylate and methacrylate and ethyl acrylate and ethacrylate polymerize on standing, especially when heated or when exposed to strong light.
2. Methyl pyruvate forms a 2,4-dinitrophenylhydrazone, M.P. 187. (dioxane and methanol as solvents).
3. Ethyl pyruvate forms a phenylhydrazone, M.P. 118.
4. On hydrolysis gives silica.
5. Reacts with β-naphthol to form β-naphthylmethyl ether, M.P. 72; with tribromophenol yields ester M.P. 87.
6. Ethyl levulinate forms a 2,4-dinitrophenylhydrazone, M.P. 101–2. (dioxane and ethanol as solvents).
7. Reacts with β-naphthol to form β-naphthylethyl ether, M.P. 37; with tribromophenol yields ester, M.P. 72.
8. Dimethyl-*d*-tartrate exists in three crystalline forms, having different melting points.
9. Dimethyl oxalate is acidic in solution and will react with concentrated ammonium hydroxide to precipitate oxamide, M.P. 417.
10. Ethyl trichloroacetate exists in three forms.
11. See also Table 42.

TABLE 11

Ethers (Liquid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density
1	Furan	1	−85.6	31.27	0.9366
2	Ethyl ether		−116.3	34.60	0.71425
3	Chloromethyl ether			59	1.020D_4^{10} (1.015)
4	Isopropyl ether		<−60	67.5	0.7247D_{20}^{20}
5	Ethylene glycol dimethyl ether			85	0.867
6	*n*-Propyl ether		−122	90.1	0.74698
7	*n*-Butyl ethyl ether		−124	92.3*	0.7505
8	α-Chloroethyl ether			98	
9	1,4-Dioxane	2	+11.8	101.4	1.03361
10	α,α′-Dichloromethyl ether			105	1.328D_4^{15}
11	β-Chloroethyl ether			107	1.057D_4^{0}
12	α,α-Dichloroethyl ether			116	1.138D_4^{12}
13	Ethylene glycol diethyl ether			121	0.8424D_{20}^{20}
14	Isobutyl ether			123	0.7616D_{15}^{15}
15	Ethylene glycol monoethyl ether	3		134.8	0.9297
16	*n*-Butyl ether		−98	142.4	0.76829
17	Anisole	4	−37.5	153.8	0.99393
18	Benzyl methyl ether			171*	0.9649
19	*o*-Cresyl methyl ether			171	0.9666
20	Ethylene glycol monobutyl ether	5		170-6N	0.9188
21	Phenetole		−33	172	0.9666
22	Isoamyl ether			172.5	0.77408D_{25}^{25}
23	*p*-Cresyl methyl ether			173	
24	*m*-Cresyl methyl ether			173	
25	1,8-Cineole ("Eucalyptol")		+1.3	176	0.9267D_{20}^{20}
26	β,β-Dichloroethyl ether			178	1.23D_{15}^{15}
27	Diethylene glycol diethyl ether			188	0.909D_{20}^{20}
28	*o*-Cresyl ethyl ether			184	
29	Benzyl ethyl ether			184-6*	0.9478
30	*n*-Amyl ether		−69.3	187.5	0.78298
31	*p*-Cresyl ethyl ether			191	
32	*m*-Cresyl ethyl ether			191	
33	Diethylene glycol monomethyl ether	6		194	1.035D_{20}^{20}
34	*o*-Chloroanisole			195	
35	Diethylene glycol monoethyl ether	7		196	1.023D_{20}^{20}
36	*p*-Chloroanisole			200	
37	Butyl phenyl ether			206	0.9515
38	Veratrole		+22.5	207	1.080
39	*p*-Chlorophenetole			212	
40	Methyl thymyl ether			216	0.954D_4^{0}
41	Resorcinol dimethyl ether		−52	217*	1.0552D_{25}^{25}
42	*n*-Hexyl ether			228	0.7936
43	Safrole		+11	233 v.s.	1.100
44	Anethole		22	235	
45	Resorcinol diethyl ether		12.4	235	
46	Eugenol methyl ether			244	1.0336
47	Isosafrole		+6.8	248	1.122

TABLE 11—*Continued*
Ethers (Liquid)

	Refractive Index	Melting Point of Derivatives (°C)			
		3,5-Dinitro-benzoate	Picrate	Bromo[a]	Others
1	1.42157				
2	1.3526	93			
3					
	1.3688	123			
5					
6	1.3885	74			
7	1.3820				
8					
9	1.4232				
10					
11					
12					
13					
14		87			
15	1.40797				
16	1.400	64			
17	1.52211		80		2,4-Dinitro 87 N
					2,4-Dibromo 61
18	1.5008				
19			116	63-64	
20	1.4177	oil		172	*p*-Nitrophenylurethan, 59
21	1.5080		92		*p*-Nitro, 58
22		61			
23			89		Anisic acid, 184
24			114		*m*-Methoxybenzoic acid, 110
25	1.45839				HBr addn. compd., 56-7
26					
27					
28			118		*o*-Ethoxybenzoic acid, 25
29	1.4958				
30	1.416				
31			111		*p*-Ethoxybenzoic acid, 196
32			115		*m*-Ethoxybenzoic acid, 137
33	1.4244				*p*-Nitrophenylurethan, 73.5
34					Nitro, 95
35	1.4298	oil			*p*-Nitrophenylurethan, 66
36					2-Nitro-4-chloroanisole, 95
37	1.5049		111		
38			57	93(di)	Nitro, 95
39					2,6-Dinitro-4-chlorophenetole, 54
40					Trinitro, 92
41			57	140(di)	2,4,6-Trinitro, 125
42					3,5-Dinitrobenzoate 55
43	1.5383		105	170(penta)	Piperonylic acid, 228
				108(tri)	Anisic acid, 184
44			70	108(tri)	
45			109	69(tri)	
46			115	*X* 78	Veratric acid, 179
47	1.5782		75	110	

[a] The letter *X* before the melting point of a bromo derivative indicates that the position of the halogen is not known. The notations of (di) and (tri) indicate the number of halogen atoms entering the molecule by addition, substitution, or both.

TABLE 11—*Continued*

Ethers (Liquid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density
48	Phenyl ether		28	259	1.073D_{20}^{20}
49	*n*-Heptyl ether			263 (260)	0.8056D_{20}^{20}
50	Isoeugenol methyl ether			264	
51	Methyl 1-naphthyl ether		<−10	271*	1.09159
52	Ethyl 1-naphthyl ether		<−10	280.5	1.0605D_{20}^{20}
53	Benzyl ether		+3.6	300 dec	1.0428

TABLE 12

Ethers (Solid)

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density
1	Isoamyl 2-naphthyl ether		28	321	
2	*n*-Amyl 2-naphthyl ether		30	322	
3	Isobutyl 2-naphthyl ether		33	304	
4	*n*-Butyl 2-naphthyl ether		33	309	
5	Ethyl 2-naphthyl ether		35-36	282	
6	Isopropyl 2-naphthyl ether		40	285	
7	*n*-Propyl 2-naphthyl ether		40	297	
8	*sec*-Butyl 2-naphthyl ether			298	
9	Hydroquinone dimethyl ether		56	213	
10	Hydroquinone diethyl ether	8	72		
11	Methyl 2-naphthyl ether		73*	273	
12	Biphenylene oxide ether (Dibenzofuran)		86	288*	
13	Allyl 2-naphthyl ether		dec	dec	
14	Benzyl 2-naphthyl ether		dec		

Notes on Ethers

1. Furan may be detected by applying it to a pine splinter which has been moistened with hydrochloric acid. A green color develops.

2. 1,4-Dioxane is soluble in water, with which it forms a constant-boiling mixture at 82.8 which contains 48 mole per cent of dioxane. Dioxane forms addition products with bromine, M.P. 65–66, and with iodine, M.P. 84–85.

3. Ethylene glycol monoethyl ether, like all glycol monoethers, gives the xanthate test for alcohols. The xanthate from ethylene glycol monoethyl ether may be purified by precipitating from a saturated solution in acetone by adding dry ether, M.P. 202.5 (cor.). For other deriv. see compd. 26 in Table 5.

4. Anisole forms a dinitro derivative which exists in two forms, M.P. 87 and 95.5. The 2,4-dibromoanisole melts at 61.

5. Compd. *b* at 170–176/743mm. See compd. 61 in Table 5 for other deriv.; it also forms the Xanthate with KOH and CS_2 (*Ind. Eng. Chem., Anal. Ed.*, 7, 128, 1935).

6. See compd. 72 in Table 5.

7. See compd. 75 in Table 5.

8. The picrate is unstable on exposure to air. With 1,3,5-trinitrobenzene addn. compd. *m* 86.5°.

TABLE 11—*Continued*
Ethers (Liquid)

	Refractive Index	Melting Point of Derivatives (°C)			
		3,5-Dinitro-benzoate	Picrate	Bromo[a]	Others
48			110	54-55(di)	
49					
50			45	101(di)	Veratric acid, 179
51	1.6940		130	*X* 46(mono)	2,4-Dibromo, 54-55
52	1.5973		119*	48(mono)	
53			78	*XX* 108(di)	

TABLE 12—*Continued*
Ethers (Solid)

	Refractive Index	Melting Point of Derivatives (°C)		
		Picrate	Bromo[a]	Others
1		94		
2		75		
3		84-85		
4		67		
5		101	66(mono)	
6		95		
7		81		
8		86		
9		48	*X* 142(di)	
10				Nitro, 49 Trinitro, 130
11		117* (113)	*X* 63(mono)	1-Nitro, 128
12		94		3-Nitro, 182
13		99		
14		123		

[a] The letter *X* before the melting point of a bromo derivative indicates that the position of the halogen is not known. The notations of (di) and (tri) indicate the number of halogen atoms entering the molecule by addition, substitution, or both.

TABLE 13
Aldehydes (Liquid)

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C) — Recommended — Semicarbazone	Melting Point of Derivatives (°C) — Recommended — 2,4-Dinitrophenylhydrazone
1	Formaldehyde (Methanal)	1	−21°	169	167
2	Acetaldehyde (Ethanal)	2	20.2	162 (169)	168.5*
3	Propionaldehyde (Propanal)		48.8	89 and 154 (α) (β)	156
4	Glyoxal		50	270	328
5	Acrolein		52.4	171	165
6	Isobutyraldehyde		64	125-6	187
7	Butyraldehyde (Butanal)		74.7	106 (95.5)	123
8	Pivalaldehyde		75	190	209
9	Isovaleraldehyde		92.5	107	123
10	Chloral		98	90*d*	
11	Crotonaldehyde		102 (104)	199 (144)	190
12	Pentanal (Valeraldehyde)		103.7		107 (98)
13	Hexanal (Caproaldehyde)		131 (128)	106	107
14	Tetrahydrofurfural		144-5 (740 mm)	166	
15	Heptanal (Enanthaldehyde)		155	109	108
16	Furfural	3	161.7	202	{230*N 214
17	Octanal (Caprylaldehyde)		171	101 (98)	106
18	Bromal		174		
19	Benzaldehyde		179	222 (214)	237
20	Nonanal (Pelargonaldehyde)		185	100 (84)	100* (96)
21	Phenylacetaldehyde	4	194	153 (156)	121N
22	Salicylaldehyde	5	197*	231	258.3* (252)
23	*m*-Tolualdehyde		199	204	
24	*o*-Tolualdehyde		200	218 (209)	194
25	*p*-Tolualdehyde		205	234	234*
26	*d*-Citronellal		207	84	77
27	*o*-Chlorobenzaldehyde		208	225 (228)	213.6*
28	*m*-Chlorobenzaldehyde		208	228	
29	Decanal (Capraldehyde)		207-9	102	104
30	Phenoxyacetaldehyde		215*d*	145	
31	Hydrocinnamaldehyde		224	127	149
32	Citral *a* (Geranial)	6	228	164N	110
33	Citral *b* (Neral)	6	228	171N	96
34	*m*-Methoxybenzaldehyde		230		
35	Cumaldehyde		236	211	244-5
36	Anisaldehyde		248	210	253-4*d*
37	Cinnamaldehyde		252	215	255*d*

Boiling under Reduced Pressure Only

	Name of Compound	Note	B. P. (°C)	Semicarbazone	2,4-Dinitrophenylhydrazone
38	Aldol	7	83_{20mm}		
39	Phenylglyoxal		108_{16}		
40	5-Hydroxymethyl-2-furaldehyde		$115\text{-}20_{0.6mm}$	195*d*	184

TABLE 13—*Continued*
Aldehydes (Liquid)

MELTING POINT OF DERIVATIVES (°C)—*Continued*

	Others				
	p-Nitrophenyl-hydrazone	Phenylhydrazone	Oxime	Methone	Others
1	181-2	145		191.4	
2	128.5	63 and 99	47	140	
3	125		40	155	
4		180	178	228	
5	150-1	52 (Pyrazoline)		192	
6	131				
7	93-5 (87)			135 (142)	
8	119		41		
9	110				
10			56		
11	185	56	119	186	
12			52	104.5	
13			51	108.5	
14			oils		α-Phenyl-α-benzylhydrazone, *m*-67
15	73		57		
16	154	97	89 and 74 (92 and 76)	160	
17	80		60	90	
18			115		
19	190 (192)	156	35	193	
20			64 (69)	86.3	
21		58 (63)	99	165	
22	227	142	57		
23	157	91	60		
24	222	101	49		
25	200.5*	114	80		
26				77-9	
27		86	75		
28		134	70		
29			69	91.7	
30		86	95		
31	123		97* (94)		
32					
33					
34	171		40		
35	190	129		170-1	
36	160-1	120-1	92	144-5*	
37	195	168	138	212-4*	

BOILING UNDER REDUCED PRESSURE ONLY—*Continued*

38	109-11			146-8	
39	309				
40	183 (185*d*)	140-1			

TABLE 14
Aldehydes (Solid)

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C) — Recommended: Semicarbazone	Recommended: 2,4-Dinitrophenylhydrazone	Others: *p*-Nitrophenylhydrazone	Others: Phenylhydrazone	Others: Oxime	Others: Methone
1	Palmitaldehyde		34	108-9		96 5		88	
2	Piperonal (*b* 263) (Heliotropin)	8	37	234	266*d*	200	102-3 (100)	110	**177-8 (193)N**
3	Stearaldehyde		38	108-9		101		89	
4	Veratraldehyde (*b* 285)		44	177	261-3*		121	94-5	
5	*o*-Nitrobenzaldehyde		44	256	250*d* (265)		156	102	
6	Lauraldehyde		44-5	106 (103)	106	90		77-8	
7	*p*-Chlorobenzaldehyde		47	230			127	106	
8	Phthalaldehyde		56				191		
9	*m*-Nitrobenzaldehyde		58	246	293*d*		120	120	
10	2-Naphthaldehyde		60	245	270	230	217 8 (206)	156	
11	*p*-Bromobenzaldehyde		67	228			113	(syn) 157 (anti) 111	
12	Vanillin		81	230	271*d**	223 (227)	105	117 (122)	196-8*
13	*m*-Hydroxybenzaldehyde		104		260*d*	221-2	147 (131)		
14	*p*-Nitrobenzaldehyde		106	221	320		159	129	
15	*p*-Hydroxybenzaldehyde	9	116-7	224 (280*d*)N	260		184 (178)	72	190* (184)
16	*β*-Resorcylaldehyde		135 6	260*d*	286*d*		159*d*	192	
17	*dl*-Glyceraldehyde		142		166-7*				
18	Protocatechualdehyde		153-4*d*		275*d*		175-6*d*	157	145*d*

TABLE 15
Ketones (Liquid)

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C) — Recommended: Semicarbazone	Recommended: 2,4-Dinitrophenylhydrazone	Others: *p*-Nitrophenylhydrazone	Others: Phenylhydrazone	Others: Oxime
1	Acetone		56	190	128	148-9	42	59
2	2-Butanone (Ethyl methyl)		80	135-6	116-7	128-9	oil	oil
3	3-Buten-2-one (Methyl vinyl)		80	141				
4	Biacetyl		89	278-9 (di)	314-5* (di)	230 (mono)	243 (di)	245-6* (di)
5	2-Methyl-3-butanone (Isopropyl methyl)		94.3	113-4	119-20	108-9	oil	oil
6	3-Pentanone (diethyl)		102	138-9	156	144	oil	69 (oil)
7	2-Pentanone (Methyl propyl)		102.3	112 (106)	143-4	117	oil	58 (oil)
8	Pinacolone		106*	157-8	125		oil	79
9	4-Methyl-2-pentanone (Isobutyl methyl)		116.8	132	95			
10	1-Chloro-2-propanone		119	164*d* (141; 150)				

TABLE 15—*Continued*
Ketones (Liquid)

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C)				
				Recommended		*Others*		
				Semicarbazone	2,4-Dinitrophenylhydrazone	*p*-Nitrophenylhydrazone	Phenylhydrazone	Oxime
11	2,4-Dimethyl-3-pentanone (Diisopropyl)		124	160*	88			34
12	2-Hexanone (Butyl methyl)		127.8	127* (122)	106-9		oil	49 (oil)
13	Mesityl oxide	10	130	164N and 133	203	132-4		48-9
14	Cyclopentanone		130.7v.s	210	146*		55	56.5
15	1-Bromo-2-propanone		136					36
16	2,4-Pentanedione (Acetylacetone)		139		209			149
17	4-Heptanone (Dipropyl)		144v s	132	75			
18	1-Hydroxy-2-propanone (Acetol)		146v s	198	128.5*	173	103	71
19	2-Heptanone (Amyl methyl)		151 2	123	89 (86)			oil
20	Cyclohexanone		155 7	166-7	162	146-7	81-2	91
21	2-Methylcyclohexanone		165	197*d*	137*			43
22	4-Hydroxy-4-methyl-2-pentanone (Diacetone alcohol)		166		202-3			58
23	Isovalerone (2,6-Dimethyl-4-heptanone) (Diisobutyl)		168	122	66 (92)			
24	2-Octanone (Hexyl methyl)		173	122-3*	58	92-3		
25	Cycloheptanone		181	163	148			23
26	5-Nonanone (Dibutyl)		188	90				
27	2,5-Hexanedione (Acetonylacetone)		194	185*d*(mono) 224(di)	257(di)		120(di)	137(di)
28	*d*-Fenchone		195-6v.s	184	140			164-5 (167)
29	Phorone (*m.p.* 28)		198	221				
30	Acetophenone (*m.p.* 19)	11	202v.s	198-9*	238-40N (250)	184-5	105	58-9
31	*β*-Thujone		202	174	114			55
32	*l*-Menthone		209	189	146		53	59
33	Isophorone		215	199 5*d*			68	79.5
34	Benzyl methyl (*m.p* 27)		216	187-190*		145	87	68-70
35	Isopropyl phenyl (Isobutyrophenone)		222	181	163		73	61-2 (94)
36	Pulegone		224	174	142			
37	1-Phenyl-2-butanone (Benzyl ethyl)		226	135				
38	6-Hendecanone (Diamyl)		228	oil				oil
39	*d*-Carvone	12	230	{162-3N {142-3	191	174-5	109-10	72-3
40	*n*-Butyrophenone		230	191	190			50
41	*p*-Chloroacetophenone		232 (236)	202-4 (160; 146)	231	239	114	95

TABLE 16
Ketones (Solid)

	Name of Compound	Note	M. P (°C)	Melting Point of Derivatives (°C) — Recommended: Semicarbazone	2,4-Dinitro-phenylhydrazone
1	1,3-Diphenyl-2-propanone (Dibenzyl) (*b.p.* 330)		34	145-6 (125-6)	100
2	*p*-Methoxyacetophenone		38	198	220
3	4-Phenyl-3-buten-2-one (*b.p.* 262) (Benzalacetone)		42 v.s.	187-8	227 (223)
4	1-Indanone (α-Hydrindone)		42 v.s.	233	258
5	Benzophenone (*b.p.* 306)		48.4	167	238-9
6	Phenacyl bromide (α-Bromoacetophenone)		50	146	
7	*p*-Bromoacetophenone		51	208	237*
8	2-Acetonaphthone		53-4	235	262*d*
9	Chalcone (Benzalacetophenone)		57	168	245*
10	Phenacyl chloride (α-Chloroacetophenone)		59		212
11	*p*-Methylbenzophenone	13	60	121-2	202.4*
12	Desoxybenzoin (*b.p.* 320)		60	148	204*
13	*p*-Methoxybenzophenone	14	62		180
14	*p*-Toluquinone		69 v.s.	178-9	269
15	1,2-Tricosanone (Laurone)		69.5	179	
16	*m*-Nitroacetophenone		81 (76)		228
17	Fluorenone		83 v.s.		283-4
18	Phenacyl alcohol		86	146	
19	Stearone		88.5		
20	Benzil		95	243-4*d* (di)	189
21	4,4-Dimethylbenzophenone (Di-*p*-tolyl)		95		229.4*
22	1,5-Diphenyl-3-pentadienone (Dibenzalacetone)		112	187-90	180
23	Quinone (Benzoquinone)	15	116 v.s.	(bis) 243*d* 166*d* (mono)	185.6 (mono)
24	1,4-Naphthoquinone (α-Naphthoquinone)		125 v.s.	245 (mono)	278 (mono)
25	Benzoin (see also under Alcohols)		133	205-6	245
26	*p*-Hydroxybenzophenone (see also under Table of Phenols)	16	135	194	242.4*
27	1,2-Naphthoquinone (β-Naphthoquinone)		145-7*d*	184*d*	
28	Furil		161-2 (165)		
29	Quinhydrone	17	171		
30	*d*-Camphor (*b.p.* 209)		179	247-8**d* (238)	177
31	Camphorquinone		199 v.s.	236*d* (147)	
32	Phenanthraquinone		208*s* (202)		312*d*
33	Anthraquinone	18	285* (275)		
34	Alizarin	19	290*		

TABLE 16—*Continued*
Ketones (Solid)

	Melting Point of Derivatives (°C)—*Continued*				
	Others				
	p-Nitrophenyl-hydrazone	Phenylhydrazone	Oxime	Methone	Others
1		128-9 (121)	125		
2	195	142	87		
3	165-7	159	117		See Table 42.
4	234-5	130-1	146		
5	154-5	137-8	143.5-4		
6			89.5 and 96.5-97		Oxidized to benzoic acid. *m* 121
7		126	128-8.5		
8		176-7	145-6		
9			140 and 68 (116 and 75)		
10					
11		109	154 and 115*N*		
12	163	116	98		
13	198-9	132 and 90	146-7 (137-8) and 115-6		
14			134-5*d*		
15		130	39-40		
16		128 (135)	132		
17	269	151-2	195-6*		
18		112	70		
19			67		
20	290	235 (di)	237		
21		100	163		
22	173		142-4		
23			140 (di)		
24	277-9*d* (mono)	205-6*d* (mono)	198 (mono)		
25		158-9	151-2		
26		144	152 and 81N		
27	236	138	169 (di) 162-4 (mono)		
28		184	100 (di)		
29					
30			118-9		
31					
32	245	165	158		
33			224*d*		
34					

TABLE 17
Acetals

	Name of Compound	B. P. (°C)	Products of Hydrolysis	
			Hydroxy	Carbonyl
1	Methylal	44	Methanol	Formaldehyde
2	Dimethylacetal	64	Methanol	Acetaldehyde
3	Ethylal	88	Ethanol	Formaldehyde
4	Acetal	104	Ethanol	Acetaldehyde
5	1,3-Dioxane	106	1,3-Propanediol	Formaldehyde
6	2-Methyl-1,3-dioxane	110	1,2-Ethanediol	Acetaldehyde
7	Isopropylacetal	122	2-Propanol	Acetaldehyde
8	Ethylpropylal	124	Ethanol	Propanal
9	Acrolein acetal	126	Ethanol	Acrolein
10	Benzaldehyde dimethyl acetal	199	Methanol	Benzaldehyde
11	Benzaldehyde diethyl acetal	222	Ethanol	Benzaldehyde

Notes on Aldehydes and Ketones

1. Commercial "formalin" is a 40% aq. solution of formaldehyde. It generally contains 10–15% methanol to prevent polymerization.

2. Acetaldehyde yields iodoform by the usual technique. This fact distinguishes it from formaldehyde or propionaldehyde. The 2,4-dinitrophenylhydrazone of acetaldehyde exists as a stable isomer which melts at 168.5 cor. and as an unstable isomer which melts at 157. A mixture of the two isomers melts about 150.

3. Furfural 2,4-dinitrophenylhydrazone exists as red crystals, m.p. 230 cor., and as yellow crystals, M.P. 212–14. A mixture of the forms melts below 200°.

4. Phenylacetaldehyde 2,4-dinitrophenylhydrazone has also been reported to have a M.P. of 110.

5. Salicylaldehydedimethone crystallizes directly as the anhydride from 70% alcohol, M.P. 208 cor. Salicylaldehyde gives the phenol test with ferric chloride.

6. Ordinary citral in the presence of $NaC_2H_3O_2$ with semicarbazide hydrochloride yields a mixture of the semicarbazones *m* 132; in the absence of $NaC_2H_3O_2$ only the geranial isomer precipitates, M.P. 164.

7. Aldoldimethone anhydride has a M.P. of 126. Aldol polymerizes to paraldol, M.P. 90; dehydrates to crotonaldehyde when distilled with $AlPO_4$.

8. Piperonaldimethone was reported to melt at 193, but a later report gives 177–8. The anhydride has M.P. 220 cor. Piperonal is readily reduced to piperonyl alcohol, M.P. 52.

9. *p*-Hydroxybenzaldehyde-2,4-dinitrophenylhydrazone crystallizes from water as red crystals, M.P. 260 and from acetic acid as purple crystals, dec. 280°.

10. Mesityl oxide semicarbazone exists as two isomers, α: M.P. 164, and β: (from benzene) M.P. 133–4.

11. Acetophenone-2,4-dinitrophenylhydrazone is reported to melt at 238–40 (from alcohol) and at 249–50° (from acetic acid).

12. *d*-Carvone semicarbazone is reported to have two melting points. When *d*-carvone, semicarbazide hydrochloride, and sodium bicarbonate are mixed in dilute alcohol, the semicarbazone melts at 162–3, whereas if *d*-carvone, potassium acetate, and a concentrated aqueous solution of semicarbazide hydrochloride stand in the cold, the product melts at 142–3.

13. *p*-Methylbenzophenone ketoxime precipitates as a mixture of isomers which can be separated by fractional crystallization by adding water to an acetic acid solution. The less soluble isomer has a M.P. of 154 and the other a M.P. of 115.

14. Oxime: α-isomer M.P. 146–7 (137–8 older ref.); β-isomer M.P. 115–6.

15. Chlorine-like odor; liberates I_2 from KI solution (acidified). Sublimes readily. Equimol. quant. with hydroquinone gives quinhydrone, M.P. 171.

16. *p*-Hydroxybenzophenone oxime exists as two isomers, M.P. 81 and 152. The lower melting isomer changes into the other by continued heating at its melting point.

17. Oxidizes to quinone, M.P. 116, readily, and reduces readily to hydroquinone, M.P. 171.

18. Several M.P. listed in literature: 273, 284–6, 285; B.P. 382. Compound boiled with NaOH soln. and Zn dust gives deep red filtrate.

19. Sublimes above 110° (differentiation from flavopurpurin and anthrapurpurin, which sublime at 160° and 170°, resp.); alizarine diacetate, from acetic anhydride and H_2SO_4 in cold, precipitated on dilution and recrystallized from alcohol, M.P. 182.

TABLE 18

Amines (Primary and Secondary—Liquid)

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C) — Recommended: Benzene-sulfon-amide	Recommended: Acet-amide	Recommended: Benz-amide	Others: *p*-Tol-uene-sulfon-amide	Others: Phenyl-thiourea	Others: α-Naph-thyl-thiourea
1	Methylamine		−6	30			75	113	192
2	Dimethylamine		7	47		41	79	135	168
3	Ethylamine		19 (16.5)	58		71	63	106 (135)	121
4	Isopropylamine		33	26				101	143
5	*n*-Propylamine		49	36		84	52	63	103
6	Diethylamine		55	42		42	60	34	108
7	Allylamine		56 (53)	39			64	98	
8	*sec*-Butylamine		63	70		76	55	101	
9	Isobutylamine		69	53		57	78	82	
10	*n*-Butylamine		77					65	108-9
11	Diisopropylamine		86						
12	Pyrrolidine		89			oil	123		
13	Isoamylamine		95					102	97
14	*n*-Amylamine		104					69	103
15	Piperidine		107 (105)	93	oil	48	96		
16	Di-*n*-propylamine		110	51	oil			69	161
17	Diallylamine		111						
18	Ethylenediamine	1	116	168	172	249	160		
19	2-Methylpiperidine	2	116			45	55		
20	1,2-Diaminopropane		120		139	192	103		
21	3-Methylpiperidine	3	126						
22	*n*-Hexylamine		128	96				77	79
23	Morpholine		130	118		75	147	136	
24	Cyclohexylamine		134		104	149			142
25	1,3-Diaminopropane		136	96	126	147	148		
26	Diisobutylamine		139	55	86			113	
27	*n*-Heptylamine		155					75	68-69
28	Di-*n*-butylamine		161					86	123
29	Ethanolamine (mono)		171						
30	1,5-Diaminopentane		178	119					
31	*n*-Octylamine		180						72
32	Aniline	4	183	112	114	160	103	154	158
33	Benzylamine		184	88	60	105	116		172
34	α-Phenylethylamine (α-amino ethyl benzene)		185			120			
35	Diisoamylamine		187					72	118
36	N-Methylaniline		194	79	102	63	94	87	
37	β-Phenylethylamine (phenethylamine)		198	69	114	116		135	
38	*o*-Toluidine		199	124	112	143	108	136	
39	*m*-Toluidine		203	95	65	125	114	94	
40	N-Ethylaniline		205	oil	54	60	87	89	
41	Diamylamine		205					72	
42	*l*-Menthylamine		207 (205)		145	156		135	
43	*o*-Chloroaniline		207	129	87	99	105	156	
44	2,4-Dimethylaniline (1,3-Dimethyl-4-amino benzene)		212	129	133 (128)	192		152 (133)	
45	N-Isopropylaniline		213		39				
46	*m*-Ethylaniline		215						

TABLE 18—*Continued*
Amines (Primary and Secondary—Liquid)

	MELTING POINT OF DERIVATIVES (°C)—*Continued*								
	Others (*Continued*)								
	β-Naphthylthiourea	α-Naphthylurea	β-Naphthylurea	3,5-Dinitrobenzoate	2,4-Dinitrobenzoate	Picrate	3-Nitrophthalimide	2-Nitro-1,3-indandione derivative	Others
1	127	197				207		203-5	
2	173	159				158		210	
3	142	200				165		202-3	
4									
5	114					135		184-5	
6	90	158		163.4*	148-9*			180-1	
7						140		180-1	
8									
9	137							178	
10	119					151			
11						140			
12									
13	116	132					90		
14	114								
15						151		182	
16	109	93						210	
17									
18	223					233		204-5	
19						135			
20									
21						138			
22									
23						146			
24	172							213	
25									
26	136	119						231	
27	115							149-50	
28						59			
29	–					160			
30									
31			99						
32	182		238*	135*					
33	173	203		210*	200	194-6*d*	143	179-80	
34								207	
35		95						190	
36			153*	122*	103*	145		186	
37						174		169	
38			232-3*	135*	190-1*	213	149-51	197-8	
39			222-3*	139-44*	142-3*	200	129-30	193-4	
40						138		183	
41	126								
42									
43							136		
44						204			
45									
46									

TABLE 18—*Continued*

Amines (Primary and Secondary—Liquid)

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C)					
				Recommended			*Others*		
				Benzene-sulfonamide	Acetamide	Benzamide	*p*-Toluene-sulfonamide	Phenyl-thiourea	α-Naphthyl-thiourea
47	2,5-Dimethylaniline		215	138	139	140	119	148	
48	*o*-Ethylaniline		216		111	147			
49	2,6-Dimethylaniline		216		176	170		204	
50	*p*-Ethylaniline		216		94	151		104	
51	3,5-Dimethylaniline		220		144	136		153	
52	N-*n*-Propylaniline		222	51	47			104	
53	2,3-Dimethylaniline		222		136	189			
54	*o*-Anisidine		225vs	89	85	60 (84)	127	136	
55	Cumidine (*p*-Isopropylaniline)		225		102	162			
56	α-Methyl-α-phenyl hydrazine		227	132	92	153			
57	Mesidine		229	137	216	204		193	
58	*o* Phenetidine		229	102	79	104 (54)		137	
59	*m*-Chloroaniline		230	121	72 (78)	120		124 (116)	
60	Tetrahydroisoquinoline		233	154	46	129			
61	Phenylhydrazine (*m.p.* 19)		243	148	128	168	151	172	
62	*m*-Phenetidine		248		97	103			
63	Tetrahydroquinoline (*m.p.* 20)		250	67	oil	75			
64	*o*-Bromoaniline (*m.p.* 29)		250		99	116		146 (161)	
65	*m*-Anisidine		251		81		68		
66	*m*-Bromoaniline (*m.p.* 18)		251		87	136 (120)		143	
67	*p*-Phenetidine		254	143	135	173	106	136	
68	Methyl anthranilate		260*d* (255)	107	101	100			
69	Ethyl anthranilate		265*d*	92	61	98			
70	2,2′-Iminodiethanol (Diethanolamine) (*m.p.* 26)	5	268						
71	*ar*-Tetrahydro-α-naphthylamine		275		158				
72	*ar*-Tetrahydro-β-naphthylamine (*m.p.* 38)		275		107				
73	Ethyl-*m*-aminobenzoate		294		110	148			
74	N-Methyl-α-naphthylamine		296		95		164 (121)		
75	Dibenzylamine		300	68		112			131
76	Diphenylamine		302	124	101	180	144	152	
77	N-Methyl-β-naphthylamine	6	315 (309)	107	51	84	78		
78	N-Ethyl-β-naphthylamine		315		49				
79	N-Ethyl-α-naphthylamine		325		68				

TABLE 18—*Continued*
Amines (Primary and Secondary—Liquid)

	Melting Point of Derivatives (°C)—*Continued*								
	Others (Continued)								
	β-Naphthylthiourea	α-Naphthylurea	β-Naphthylurea	3,5-Dinitrobenzoate	2,4-Dinitrobenzoate	Picrate	3-Nitrophthalimide	2-Nitro-1,3-indandione derivative	Others
47						170			
48								183	
49						180			
50								181	
51						200*d*			
52								190-1	
53						221*d*			
54						200	184-6		
55									
56									
57									
58							164		
59							171-3		
60						200			
61									
62									
63									
64						165			
65							158		
66						187			
67							173		
68									
69			165-7						
70						110			
71									
72									
73									
74									
75								203	
76			158						
77						145			
78									
79									

TABLE 19

Amines (Primary and Secondary—Solid)

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C)				
				Recommended			Others	
				Benzene-sulfon-amide	Acetamide	Benzamide	*p*-Toluene-sulfon-amide	Phenyl-thiourea
1	*m*-Iodoaniline		27		119	157	128	
2	2,2′-Iminodiethanol (Diethanolamine) (*b* 268)	5	28					
3	*o*-Bromoaniline (*b.p.* 250)		31		99	116		146
4	*as*-Diphenylhydrazine		34		184	192		
5	N-Benzylaniline (*b* 298)		37	119	58	107		103
6	*ar*-Tetrahydro-*β*-naphthyl-amine		38		107			
7	Ephedrine (1-Phenyl-2-methylaminol-1-propanol)	7	39					
8	*p*-Amino-N,N-dimethyl-aniline (*b* 262)		41		130	228		
9	4-(N-Methylamino)-2-nitrotoluene		45		128			
10	2,4′-Diaminobiphenyl		45		202	278		
11	*p*-Toluidine (*b* 200)		45	120	153	158	117	141
12	2-Aminobiphenyl (*o*-Aminodiphenyl)		49 (45)		119	86 (102)		
13	*α*-Naphthylamine		50	167	159	160	157	165
14	2,5-Dichloroaniline		50		132	120		
15	Indole (*b* 253)	8	52	254		68		
16	4-Aminobiphenyl		53		171	230		
17	Diphenylamine	9	54	124	101	180	141	152
18	*o*-Iodoaniline		56 (58)		109	139		
19	*p*-Anisidine (*b* 240)		58	95	127	154 (157)	114	157
20	2-Aminopyridine		60		71	165		
21	*p*-Iodoaniline		62		183	222		153
22	N-Phenyl-*α*-naphthylamine		62		115	152		
23	*m*-Phenylenediamine	10	63	194	191	240	172	
24	2,4-Dichloroaniline		63	128	145	117	126	
25	*p*-Tolylhydrazine		65		121	146		
26	*p*-Bromoaniline (*b* 245)		66	134	167	204		148
27	Pseudocumidine		68	136	161	167		
28	*p*-Chloroaniline (*b* 230)		70 (72)	122	179 (172)	192	95 (119)	152
29	*o*-Nitroaniline		71 v.s.	104	92	94		142
30	4-Nitromesidine		75	163	191	169		
31	4-Aminodiphenylamine (anhydrous)		75		158	203		
32	4-Amino-2-nitrotoluene		77 (72)	160	148 (93)	172	164	
33	2,4,6-Trichloroaniline	11	78		204	174		
34	2,4-Dibromoaniline		79		146	134	134	
35	Ethyl *p*-aminobenzoate		90		110	148		
36	*p*,*p*′-Diaminodiphenyl-methane	24	94		228			
37	Semicarbazide		96		165	225		
38	2,4-Diiodoaniline		96			181		
39	*o*-Phenylenediamine	11	102	185	185	301	201	
40	Piperazine (*b* 140)	23	104	282(di)	144(di) (134)	196(di) (191)	173(mono)	
41	*p*-Aminoacetophenone		106	128	167	205	203	
42	*p*-Bromophenylhydrazine		106					
43	N-Phenyl-*β*-naphthylamine		108		93	148 (136)		

TABLE 19—*Continued*

Amines (Primary and Secondary—Solid)

	Melting Point of Derivatives (°C)—*Continued*								
	Others (Continued)								
	α-Naphthylthiourea	β-Naphthylthiourea	α-Naphthylurea	β-Naphthylurea	3,5-Dinitrobenzoate	2,4-Dinitrobenzoate	Picrate	3-Nitrophthalimide	2-Nitro-1,3-indandione derivative
1									
2							110		
3							165		
4									
5					133*	122*			
6									
7									
8									
9									
10									
11				266-7*	145-7*	159	182	156	192-3
12									
13				249-50*	200.5*	199.5	163	223	209-10
14									
15									
16				259-60*					
17						unstable			
18									
19							170	197	
20									
21									
22									
23					158 7*	197.5*			200
24									
25									
26				286-8*				202	
27									
28				280-1	133*	165*	187	199	
29				203-5*				171	
30									
31									
32									
33									
34									
35									
36									248
37									
38									
39					177.3*	198*			172-4
40							280		
41									
42									
43									

TABLE 19—*Continued*

Amines (Primary and Secondary—Solid)

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C)				
				Recommended			*Others*	
				Benzene-sulfon-amide	Acetamide	Benzamide	*p*-Toluene-sulfon-amide	Phenyl-thiourea
44	*β*-Naphthylamine		112 (110)	102	132	162	133	129
45	*m*-Nitroaniline		114	136	155	155 (158)	138	160
46	3-Nitro-4-aminotoluene		117	102 (99)	99 (96)	148 (143)	146 (166)	
47	2,4,6-Tribromoaniline	11	119		232 (mono)	198		
48	*m*-Hydroxyaniline (*m*-Aminophenol)	12	122		148 (mono)	153	157	156
49	*p*-Aminoazobenzene	23	127 (125)		146	211		
50	Benzidine		127	232(di)	317(di)	352(di)	243(di)	
51	*o*-Tolidine		129 (124)		314(di)	265(di)		
52	2-Amino-5-nitrotoluene		130	158	198	174		
53	*p*-Acetophenetidine	13	135 (138)					
54	3-Amino-6-nitrotoluene		135		102			
55	2,6-Dinitroaniline		138		197			
56	*p*-Phenylenediamine		140	247(di)	204(di)	300	266(di)	
57	Anthranilic acid (see Amino Acids)		145 (147)	214	185	182		
58	*p*-Nitroaniline		147	139	215	199	191	
59	*p*-Nitrophenylhydrazine		157*d*		205	193		
60	*p*-Aminoacetanilide		162		304			
61	Picramic acid	23	169		201	230 (220)	191	
62	*o*-Hydroxyaniline (*o*-Aminophenol)		174	141	201	182(di)	139	146
63	*m*-Aminobenzoic acid (see Table of Amino Acids)		174					
64	2,4-Dinitroaniline		180		120	202 (220)	219	
65	*p*-Hydroxyaniline (*p*-Aminophenol)	14	184*s*	125	168(mono) 150(di)	234(di)		150
66	*p*-Aminobenzoic acid (see Table of Amino Acids)		186 (188)					
67	2,4,6-Trinitroaniline (Picramide)	15	190	211	230	196		
68	1-Amino-4-nitronaphthalene		195	158	190	224	185	
69	2,4-Dinitrophenylhydrazine		198*d*		197	206		
70	Carbazole		243		69	98		
71	*m*-Aminoacetanilide		279		191			
72	2-Aminoanthraquinone		302	271	257	228	304	

TABLE 19—*Continued*

Amines (Primary and Secondary—Solid)

	MELTING POINT OF DERIVATIVES (°C)—*Continued*								
	Others (Continued)								
	α-Naphthyl-thiourea	β-Naphthyl-thiourea	α-Naphthyl-urea	β-Naphthyl-urea	3,5-Dinitro-benzoate	2,4-Dinitro-benzoate	Picrate	3-Nitro-phthal-imide	2-Nitro-1,3-indan-dione derivative
44				310-2*	157*	181 5*	195	212	193
45				222-5*	112-4*	133*		219	
46									
47									
48									
49									
50				> 320	205.7*	232-3*			213
51									216
52									
53									
54									
55									
56				> 320	178*	182*			261-3
57							104		
58				275-6*	128.6*	118*		255	
59									
60									
61									
62				191-3*					
63									
64									
65				256*	178 5*	204.5*			
66									
67									
68									
69									
70							185		
71									
72									

TABLE 20

Amines (Tertiary—Liquid)

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C)							
				Recommended		*Others*					
				Picrate	Quaternary methyl iodide	Methyl-*p*-toluene sulfonate	Chloroplatinate	3,5-Dinitrobenzoate salt	2,4-Dinitrobenzoate salt	*p*-Toluene sulfonate salt	Others
1	Trimethylamine		3	216 (225)	230*d*					162	
2	Triethylamine		89	173				138-150*	81-3*	liq	
3	Pyridine		116	167	117	139	241	171*	141*	160	
4	α-Picoline		129	169	230 (224)	150	195*d*			161	
5	β-Picoline	16	143	150							
6	γ-Picoline		143	167							
7	Tri-*n*-propylamine		153	116							
8	2-Chloropyridine		166			120					
9	*d*-Coniine		170	75			175 (anh.) 78 (hyd.)				
10	N,N-Dimethylaniline		193 (196)	163	228*d* (220)	161	173*d*	115*	104*	133	
11	Ethylmethylaniline		201	134	125						
12	Diethyl-*o*-toluidine		206	180	224*d*						
13	Tributylamine		211		180						
14	Dimethyl-*p*-toluidine		211	129	219	85					
15	Dimethyl-*m*-toluidine		212		177						
16	Diethylaniline		218	142	102						
17	Quinoline	17	239	203	133 (anh.) (72)	126	218	152*	142.5*	155	
18	Isoquinoline (*m.p.* 24)	18	240	222	159	163	263*d*				
19	*dl*-Nicotine		242	218							Oxidized to nicotinic acid
20	Dipropylaniline		245		156						
21	Triisoamylamine		245	125							
22	Quinaldine		247	191	195	161	226				
23	Tri-*n*-amylamine		257			80*d*					
24	6-Methylquinoline		258	229	219(216)	154					
25	Lepidine (4-Methylquinoline)		263								
26	2,4-Dimethylquinoline		264	194	252						
27	N,N-Di-*n*-butylaniline		271	125		180					
28	Dimethyl-α-naphthylamine		272								
29	Methyldiphenylamine		296								
30	6-Methoxyquinoline *m.p.* 28 (20)		305*d*								

TABLE 21

Amines (Tertiary—Solid)

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C)				
				Recommended		Others		
				Picrate	Quaternary methyl iodide	Methyl *p*-toluene sulfonate	Chloroplatinate	Others
1	Isoquinoline (*b* 240)	18	24	222	159	163	263*d*	
2	6-Methoxyquinoline (*b* 305*d*)		28 (20)					
3	2,6-Dimethylquinoline		60	178	237	175		
4	*m*-Nitrodimethylaniline		60	119	205			
5	Phenylpyrrole		61					
6	Dibenzylaniline		70 (67)	131*d*	135			
7	8-Hydroxyquinoline		75	204	143*d*			
8	*p*-Nitrosodimethylaniline	19	85	140				
9	Tribenzylamine	20	91	190	184			
10	Acridine		108	208				
11	Antipyrine		113					
12	*p*-Dimethylaminoazobenzene		117		174			
13	Triphenylamine	21	127					
14	Methyleneaminoacetonitrile	22	129					
15	6-Nitroquinoline		149		245			Hydrobromide, 245
16	6-Nitroquinaldine		164					
17	*p,p'*-Bis(dimethylamino)-benzophenone		174	156	105			
18	2-Hydroxyquinoline		199					
19	Hexamethylenetetramine		(280) subl.	157 179*d*				Dibromide, 198-200

Notes on Amines

1. Hydrate with 1 H_2O, M.P. 10.
2. Hydrochloride, M.P. 210.
3. Hydrochloride, M.P. 172.
4. Hydrochloride, M.P. 198.
5. Nitrate, M.P. 69.
6. With HNO_2 yields N-nitroso derivative, M.P. 88.
7. Hydrochloride, M.P. 216.
8. N-nitroso derivative, M.P. 171.
9. Yields readily N-nitroso derivative, M.P. 67.
10. Disubstituted derivatives obtained with difficulty.
11. Acetyl derivative easily prepared.
12. Diacetyl derivative, M.P. 101.
13. Nitration gives 3-nitro derivative, M.P. 103, which on hydrolysis yields nitrophenetidine, M.P. 113.
14. Monoacetyl derivative, M.P. 168; diacetyl derivative, M.P. 150. Compound melts with decomposition.
15. Forms with naphthalene in acetic acid, addition compound, M.P. 168.
16. Oxidizes to nicotinic acid, M.P. 228.
17. Yields ethiodide, M.P. 159.
18. Yields ethiodide, M.P. 148.
19. Hydrochloride, M.P. 177.
20. Ethiodide, M.P. 190.
21. Nitrated with fuming HNO_3 in acetic acid yields trinitro derivative, M.P. 280.
22. Acid hydrolysis gives glycine.
23. See also Table 42.
24. See deriv. with acids, pp. 206, 212.

TABLE 22

Amides[a]

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C)		
				N-Xanthyl derivative	Mercury derivative	Oxalate
	Liquids					
1	Formamide		195*d*			107.5*
2	Formylpiperidine		222			
3	Acetylpiperidine		226			
	Solids		M. P. (°C)			
4	Formanilide		46 (50)			
5	Ethyl carbamate		49			
6	N-Propylacetanilide		50			
7	Methyl carbamate		52			
8	Butyl carbamate		54			
9	N-Ethylacetanilide		54			
10	Isobutyl carbamate		55			
11	Caprylanilide		56			
12	Propyl carbamate		60			
13	*n*-Valeranilide		62			
14	Allylurea		80			
15	Propionamide		81	210-11	201	81*
16	Acetamide		82	238 40	196-97	127*
17	Acetacetanilide		85			
18	Isopropyl carbamate		92			
19	*m*-Toluamide		94		200	
20	Stearanilide		95			
21	Heptamide		96	154-5		
22	*n*-Butyramide		96			
23	Semicarbazide	1	96			
24	Capramide		99			
25	Lauramide		100			
26	Methylurea	2	101			
27	Caproamide		101	159-160		71*
28	Myristamide		103			
29	Propionanilide		105			
30	Isobutyranilide		105			
31	Palmitamide		105	140-142		
32	Caprylamide		106			
33	*sym*-Dimethylurea		106			
34	*n*-Valeramide		106	166-7		61
35	Stearamide		109			139 141
36	Acetanilide		114			
37	Ethyl oxamate		114			
38	Butyramide		115	185-87	222-4	66
39	Chloroacetamide		120	208-09		
40	Furoanilide		123			
41	Succinimide		126	245-47		
42	*p*-Methoxyacetanilide		127			
43	*o*-Anisamide		128		241	
44	Isobutyramide		129	210-11		
45	Nicotinamide	9	129			
46	Piperine		129			
47	Benzamide		130	223	222	
48	Urea	3	132			
49	*dl*-Mandelamide		133			
50	Phenacetin		135			
51	Isovaleramide		136			183

[a] Sulfonamides are listed separately under sulfur compounds; amides and anilides are also listed in tables 1-4.

TABLE 22—*Continued*

Amides

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C)		
				N-Xanthyl derivative	Mercury derivative	Oxalate
52	Salicylamide		142 (139)		190	
53	*m*-Tolylurea		142			
54	Furamide		142	209-11		
55	*o*-Toluamide		143 (158)	199-200	196	
56	Trichloroacetamide		145			
57	*p*-Toluanilide		145			
58	Phenylurea		147			
59	Diphenylguanidine		147			
60	Cinnamamide		148 (142)			
61	Benzylurea		149			
62	Cinnamanilide		151			
63	α-Phenylacetamide		154	194		
64	Benzilamide		154			
65	*o*-Bromobenzamide		155		242	
66	*m*-Bromobenzamide		155		235	
67	*o*-Toluamide		158 (143)	199-200	196	
68	Isocaproamide		159-160			
69	*p*-Toluamide		160 (166)	224-25	260	
70	Benzanilide		160			
71	*p*-Anisamide		167		222	
72	*p*-Bromoacetanilide		167			
73	*p*-Anisanilide		169			
74	Alloxan	4	170*d*			
75	Malonamide		170			
76	Glutaramide		175			
77	*o*-Nitrobenzamide		176			
78	*p*-Chloroacetanilide		179			
79	Maleamide		181			
80	*p*-Tolylurea		181			
81	Dimethylurea (unsym.)	5	182			
82	*p*-Iodoacetanilide		182			
83	3,5-Dinitrobenzamide		183			
84	*m*-Iodobenzamide		186			
85	Hippuric acid, see p. 364 (101)		187			
86	Diethylbarbituric acid		188			
87	*p*-Bromobenzamide		189		266	
88	*as*-Diphenylurea		189			
89	*o*-Tolylurea		192			
90	Biuret		192*d*			
91	β-Naphthoamide		195			
92	Isatin		200			
93	*p*-Nitrobenzamide		201	231-33		
94	Ethylisopropylbarbituric acid		201			
95	α-Naphthoamide		202			
96	Dicyanodiamide		207			
97	Sebacamide		210			
98	*p*-Nitroacetanilide		212			
99	*p*-Iodobenzamide		217			
100	Acetylurea		218			
101	Hydantoin	9	218			
102	Phthalamide	10	220di			
103	Adipamide		220			
104	Saccharin	6	220 (199)			
105	*dl*-Tartaramide		226			
106	Succinanilide		230			
107	Phthalimide	12	234 (238, 228)	176-177		

Amides

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C)		
				N-Xanthyl derivative	Mercury derivative	Oxalate
108	Caffeine	7, 9	234			
109	Carbanilide (*s*-Diphenylurea)		238 (240)			
110	Barbituric acid	9	245 (254)			
111	Succinamide		250 (255)			
112	Oxanilide		257			
113	Theophylline	9	264 (274)			
114	N,N′-Diacetyl-*p*-phenylene-diamine		300			
115	Theobromine	9	subl. 337			
116	Xanthine	9	360			
117	Uric acid	8, 9	400*d*			
118	Oxamide	11	419*d*			

Notes on Amides

1. Semicarbazide is easily derivatized by use of carbonyl compounds, such as acetone and the like.
2. It forms a picrate, M. P. 127*d*.
3. It forms a picrate, M. P. 148. Treated in very dilute solutions of acetic acid (50%) with xanthydrol dissolved in alcohol forms deriv., M. P. 265 (dixanthylurea). For tests and details as to deriv., see *urea* in Table 42.
4. On oxidation gives alloxantin, M. P. hydrate 201-3.
5. Picrate, *m* 130*d*.
6. Forms xanthyl derivative, M. P. 199 (see page 325–6).
7. Aqueous solution of compound forms with sat. soln. of $HgCl_2$ deriv. M. P. 246 (corr.).
8. On oxidation with dilute nitric acid gives alloxan, M. P. 170*d*.
9. See Table 42.
10. Monoamide: *m* 149.
11. M. P. detn. in sealed tube.
12. See page 454.

TABLE 23
Amino Acids

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C): Recommended		Others	
				p-Toluene-sulfonyl	Phenylurea	Benzoyl	Acetyl
1	N-Phenylglycine		126		195	63	194
2	*d*- or *l*-Ornithine	1	140		190	240(mono) 189*(di)	
3	Anthranilic acid (*o*-Aminobenzoic acid)		145 (147)		181	182	185
4	*m*-Aminobenzoic acid		174		270	248	250
5	Canavanine ($C_5H_{12}O_3N_4$)		182-3			86*d*	
6	*p*-Aminobenzoic acid		186		300	278	252
7	*β*-Alanine		196		168 (174)		
8	*dl*-Glutamic acid		199 (192)			155-7*	
9	*l*-Isoserine		200*d*			107-9*	
10	*dl*-Proline		203		170		
11	*d*-Arginine	2	207			298(mono) 235(di)	
12	Sarcosine		210		102		135
13	Canaline ($C_4H_{10}O_3N_2$)		214*d*			99	
14	*β*-Hydroxyvaline		218*d*		182	153(mono)	
15	*l*-Proline	3	222*d*	130-3	170N	156(mono)	
16	*d*- or *l*-Glutamic acid	4	224**d*N	115-7		130-2	
17	*d*- or *l*-Lysine		224*d*			149-50(di)	
18	*l*-Citrulline ($C_6H_{13}O_3N_3$)		226				
19	*d*- or *l*-Asparagine		227*d*		164		
20	*β*-Hydroxynorvaline ($C_5H_{11}O_3N$)		230-1*d*		156	170-1(mono)	
21	*dl*-Thyroxine	5	231-3N				
22	Glycine	6	232	150 (147) (146)	197* (163)	187.5	206
23	*dl*-Arginine		238				
24	*dl*-Threonine (*α*-Amino-*β*-hydroxybutyric)	7A	239*d*		177-8	176(mono)N 174(di)	
25	*dl*-Serine		246	213*d*	169	171(mono) 124(di)	
26	*dl*-Isoserine		248*		184	151*	
27	*p*-Hydroxyphenylglycine		248			117	203
28	*d*- or *l*-Threonine	7A	253			176(mono) 174(di)	
29	*l*-Cystine ($C_6H_{12}O_4N_2S_2$)	7B	260*d*	204-5*(di)	160	181(di)	
30	*dl*-Phenylalanine	8	264*d*N	134-5	182	188*	
31	*l*-Glycylglycine		264		176		
32	*l*-Hydroxyproline		270	153	175	100(mono) 92(di)	
33	*d*- or *l*-Aspartic acid		270-2	140	162	185*	
34	*d*- or *l*-Allothreonine		272			128	
35	*dl*-Methionine		272	105		151	114
36	*dl*-Aspartic acid		280			165*	
37	*l*-Methionine		283*d*				
38	*d*- or *l*-Isoleucine (*s*230)		284*d* (279)	130-2	120	117	
39	*l*-Histidine		288 (253)	202-4*d*		230*d*(mono)	

TABLE 23—*Continued*

Amino Acids

	Melting Point of Derivatives (°C)—*Continued*							
	Others (Continued)							
	Formyl	Picrate	Picrolonate	α-Naphthyl-urea	3,5-Dinitro-benzoyl	β-Naphtha-lene-sulfonyl	Phenyl-hydantoin	Others
1	125							
2		208 (mono and di)				189		Flavianate, 234-5
3		104			278			
4					270			
5		163-4						Flavianate, 210-5; Cu salt, 205-7
6					290			
7					202-5			
8			184*d*				165*	G·HCl, 202*d*
9								
10		135-7			217		118*	
11		270(mono) 200(di)	235*d*(mono)		[150]	87-9		Flavianate, 258-60*d* (mono); 220(di)
12					153-5			
13		192						Flavianate, 211*d*; C·HCl, 166*d*
14							125	
15		154				138(anhyd) [+H_2O, 133-7]	144	Reineckate, 199*d*
16			184	236-7	softens and shrinks, 98-9			G·HCl, 193
17		266	246-52				183-4*	Flavianate, 213*d*; L·HCl, 193
18								Cu salt, 257-8
19		180*d*		199	196			
20							154-5	
21								Methyl ester, 156
22	153-4	200	214-5*d*	191	179	159*		
23		232	248 (231)			85 (85-120) (not sharp)		
24							164-5	
25			265*d*	192	95	214* (220)	168-9	
26								
27								
28								
29					180*d*	226-30	117	
30		173	238N (182, 212)	143-4		173-4		
31					210	180-2		
32							123-4	
33				115*d*		153		
34								
35								
36			130*d*					
37	98-9		178	188	150(anh.) 94-5(hyd.)			
38			170 (not sharp)	178*d*				
39		86	232(mono) 265*d*(di)		189	149-50		Flavianate, 224-6*d*; Reineckate, 220*d*

Amino Acids

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives (°C): Recommended: *p*-Toluene-sulfonyl	Recommended: Phenylurea	Others: Benzoyl	Others: Acetyl
40	*l*-Tryptophane		290	176	166		
41	*dl*-Isoleucine		292	141*		118	
42	*d*-α-Aminobutyric acid		292*d*			121	
43	*dl*-Alanine		293*d*	139	174*d* (190)	166*	
44	*d*- or *l*-Alanine		297*d*	133 (92-94)	175*d*	151*	116
45	*dl*-Valine		298	110	164	132	
46	*d*-Norleucine (*s*275)		301				
47	Creatine		303				
48	Creatinine		305*d*				
49	*l*-Norvaline		305				
50	*dl*-α-Aminobutyric acid		307		170	147	
51	*d*- or *l*-Valine (subl.)		315*	147	147		
52	*l*-Tyrosine	9	314-8*d* (290, 334)	188*(mono) 114(di)	104 194(di)	166-7 211-2(di)	
53	*d*- or *l*-Phenylalanine	10	280 (320N)	164-5* (161)	181*	146*	
54	*dl*-Norleucine		327	124			
55	*dl*-Leucine		332		165	137-41* (mono)	
56	*d*- or *l*-Leucine		337	124*	115	105-7* (mono)	
57	*dl*-Tyrosine	9	340			197(mono) (166)(mono)	
58	Djenkolic acid ($C_7H_{14}O_4N_2S_2$)		300-50*d*			85(di)	
59	*dl*-Ornithine (cryst.)	1		188(mono)	192	267(mono) 188*(di)	
60	*dl*-Lysine (solid)				196	249(mono) 146(di)	
61	*dl*-Norvaline		303* (closed capillary)		117		
62	*l*-Cysteine ($C_3H_7O_2NS$) oxidized to *l*-Cystine, m. 260, q.v.		none				

Notes on Amino Acids

1. No melting point is given in any of the standard works including *Beilstein* 2nd Suppl. (1942). *d*-Ornithine is listed as a syrup. The M. P. of 140° listed was obtained from Vickery and Cook, *J. Biol. Chem.* **94**, 398 (1931).

2. The M. P. of *d*-arginine, 207° is often confused with the M. P. of *dl*-arginine, 238°. For the Picrolonate of *d*-arginine see Heyl, *J. Am. Chem. Soc.*, **41**, 681 (1919).

3. The *l*-proline phenylurea deriv. may ppt. as a resin, and should be converted to the hydantoin which melts at 118° (144).

4. The M. P. of *d*-glutamic acid depends on the rapidity of heating and the temperature of drying. The pure benzoyl derivative melts at 130-132; values of 139° are most likely melting points of impure derivatives.

5. Thyroxine melts at 250° when heated 10°/min.; at 230-5° when heated 3°/min.; iodine is evolved in all cases.

6. Glycine picrate contains 2 mol. of glycine; it softens at 199-200° and decomposes at 202°. The earlier figure of 190° is stated to be erroneous. The barium salt crystallizes even from dilute solutions and is suitable for separation from other amino acids.

7A. The dibenzoyl derivative melts at 174°, the monobenzoyl at 176° and the eutectic of the two at 145°.

7B. The phenylurea deriv. gives hydantoin, *m* 117.

8. Variable values are given in the literature for the decomposition point of the pure compound and of the picrolonate.

9. The di-β-naphthalenesulfonyl derivative of *l*-form gives at 100-102° a viscous oil. It is very slightly soluble in hot water and very soluble in hot alcohol. *dl*-Tyrosine quickly heated decomposes at 340°; but in a preheated bath at 295°. Forms both di and mono-derivatives. See Footnote 18, McCherney and Swann, *J. Am. Chem. Soc.*, **59**, 1117. The M. P. of *l*-tyrosine has been confused in some works with the M. P. of *dl*-form. The decomposition point of the *l*-form with rapid heating is 314-8°, and with slow heating 290-5°, (Fischer, *Ber.* **32**, 3641).

10. The decomposition point is variously given as 283°, 275-80° and 320°.

TABLE 23—*Continued*
Amino Acids

	Melting Point of Derivatives (°C)—*Continued*							
	Others (Continued)							
	Formyl	Picrate	Picrolonate	α-Naphthyl-urea	3,5-Dinitro-benzoyl	β-Naphtha-lene-sulfonyl	Phenyl-hydantoin	Others
40		195-6	203-4	159-60	233*d*	185		
41								
42				195		148	120-7*d*	
43			216*d*	198	177	152-3*		
44		none	217*d*(mono) 145(di)	202*d*		122-3		
45	145		150(quick) 220(slow)				125	
46						149		
47								
48		220						
49	137							
50				194			126	
51	146		170-80		157-8		131-3	
52	147(di)		260*d* (mono)	205-6 (mono)		102-22N(di)		
53	167		208*d*	155	93			
54	114							
55			150*d*(quick) 188*d*(slow)			145-6		
56			150		186-7	68*	163.5	
57			260*d*	205-6	252-4 (di)			
58								Dihydantoin, 200
59		203(di)	221*d*(mono) 236(di)					
60		225*d*(mono)						L·HCl, 192-3
61	132*						103	
62								

TABLE 24

Alkyl and Cycloalkyl Halides[a]

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C) Recommended: S-Alkyliso-thiourea picrate	Naphthalide
	Chlorides				
1	Methyl		−22 (−24)	224	160
2	Vinyl		−14		
3	Ethyl		12	188	126
4	Propenyl		36		
5	Isopropyl		36	196 (148)	
6	Allyl		44.6	155	
7	*n*-Propyl		46	181 (176)	121
8	*tert*-Butyl		51		147
9	Chloromethyl ether		59		
10	*sec*-Butyl		67	190 (166)	129
11	Isobutyl		68	174	125
12	*n*-Butyl		77	180 (177)	112
13	Neopentyl		85		
14	*tert*-Amyl		86		138
15	α-Chloroethyl ether		97		
16	Isoamyl		100	179 (173)	111
17	α,α′-Dichloromethyl ether		105		
18	*n*-Amyl		107	154	112
19	α,α′-Dichloroethyl ether		116		
20	*n*-Hexyl		134	157	106
21	Cyclohexyl		142		188
22	*n*-Heptyl		160		95
23	β,β′-Dichloroethyl ether		178		
24	Benzyl	1	179	188	166
25	Octyl		184		91
26	Phenethyl (β-Phenylethyl)		190		
27	α-Chloroethylbenzene (α-Phenylethyl)		195		
28	β-Chlorostyrene		199		217
29	*p*-Chlorobenzyl	2	214		
30	Cetyl		289*d*	155	
31	*p*-Bromobenzyl (*m.p.* 36)	3		219	
32	Triphenylmethyl (*m.p.* 113)	4			
	Bromides				
33	Methyl		5	224	160
34	Vinyl		16		
35	Ethyl		38	188	126
36	Propenyl		60		
37	Isopropyl		60	196 (148)	
38	Allyl		71	155	
39	*n*-Propyl		71	181 (177)	121

[a] In this table are included a few halogen ethers that are likely to be detected in class tests for alkyl or aryl halides rather than as ethers.

TABLE 24—*Continued*
Alkyl and Cycloalkyl Halides

	Melting Point of Derivatives (°C)—*Continued*					
	Others					
	Anilide	Alkylmercuric halide	Alkyl β-Naphthyl-ethers (and their picrate)	Alkyl-3-nitro-phthalimide	Alkyl-saccharin	2,4,6-Triiodo-phenyl ester
1	114	167*	70	113	132	
2	104					
3	104	192	37 (Picrate, 104)	106	94	
4	114					
5	103		41 (Picrate, 92)		134	
6	114					
7	92	147*	39 (Picrate, 75)	85	74	
8	128					
9						
10	108				81	
11	109				95	
12	63	130		72	38	
13	86					
14	92					
15						
16	108	86		94		
17						
18	96	110*			58	
19						
20	69	125*				
21	146					
22	57	119.5*				
23						
24	117		99	143		122
25	57					
26	97					
27	133					
28	115					
29	166					
30		102		101	98	
31						
32						
33	114	172*	70	113	132	
34	104					
35	104	193 (198)	37 (Picrate, 104)	106	94	83-84
36	114					
37	103	93	41 (Picrate, 92)		134	43
38	114					
39	92	140	39 (Picrate, 75)	85	74	82

TABLE 24—*Continued*

Alkyl and Cycloalkyl Halides

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives (°C)	
				Recommended	
				S-Alkyliso-thiourea picrate	Naphthalide
40	*tert*-Butyl		72		147
41	*sec*-Butyl		90	190 (166)	129
42	Isobutyl		91	174 (167)	125
43	*n*-Butyl		100	180 (177)	112
44	*tert*-Amyl		108		138
45	Neopentyl		109		
46	Isoamyl		118	179 (173)	111
47	*n*-Amyl		129	154	112
48	*n*-Hexyl		157	157	106
49	Cyclohexyl		165		188
50	*n*-Heptyl		174	142	95
51	Benzyl		198	188	166
52	Octyl		204	134	91
53	α-Bromoethylbenzene (α-Phenylethyl)		205		
54	Phenethyl (β-Phenylethyl)		218		
55	β-Bromostyrene		221		217
56	Cetyl (*m.p.* 16)			155	
57	*p*-Chlorobenzyl (*m.p.* 49)	2		194	
58	*p*-Bromobenzyl (*m.p.* 62)	3		219	
	Iodides				
59	Methyl		43	224	160
60	Vinyl		56		
61	Ethyl		72	188	126
62	Ethylene		82	270	
63	Isopropyl		89	196 (148)	
64	*tert*-Butyl		98	188	147
65	*n*-Propyl		102	181 (176)	121
66	Allyl		103	155	
67	*sec*-Butyl		119	190 (166)	129
68	Isobutyl		120	174 (167)	125
69	*tert*-Amyl		128		138
70	*n*-Butyl		130	180	112 (110)
71	Isoamyl		148	179 (173)	111
72	*n*-Amyl		156	154	112
73	*n*-Hexyl		180	157	106
74	*n*-Heptyl		204	142	95
75	Cetyl (*m.p.* 22)			155 (137)	
76	Benzyl (*m.p.* 24)			188	166

TABLE 24—*Continued*
Alkyl and Cycloalkyl Halides

	Melting Point of Derivatives (°C)—*Continued*					
	Others					
	Anilide	Alkylmercuric halide	Alkyl β-Naphthyl ethers (and their picrate)	Alkyl-3-nitro-phthalimide	Alkyl-saccharin	2,4,6-Triiodo-phenyl ether
40	128					
41	108	39			81	
42	109	55			95	48
43	63	136		72	38	66
44	92					
45	126					
46	108	80		94		
47	96	127			58	47
48	69	127.5				44-45
49	146	153				
50	57	118.5*				
51	117	119	99	143		
52	57	109				
53	133					
54	97	169				88
55	115	91				
56		101.5		101	98	
57						
58						
59	114	152	70	113	132	98-99
60	104					
61	104	186	37 (Picrate, 104)	106	94	
62			148		99	
63	103		41 (Picrate, 92)		134	
64	128					
65	92	113*	39 (Picrate, 75)	85	74	
66	114					
67	108				81	
68	109	72			95	
69	92					
70	63	117		72	38	
71	108	122		94		
72	96	110*			58	
73	69	110*				
74	57	103*				
75		82		101	98	
76	117		99	143		

TABLE 25
Aromatic[a] Halides (Liquid)

	Name of Compound	Note	B. P. (°C)	Melting Point of Derivatives: Recommended — Nitro: Position	Nitro: M. P. (°C)	Others: Name	Others: M. P. (°C)
1	Fluorobenzene		85			4,4′-Difluorodiphenylsulfone	98
2	*p*-Fluorotoluene		117			*p*-Fluorobenzoic acid	186
3	Chlorobenzene		132	2,4	52		
4	Bromobenzene		157	2,4	75 (72)	α-Naphthalide	161
5	*o*-Chlorotoluene		159	3,5	63	*o*-Chlorobenzoic acid	140
6	*m*-Chlorotoluene		162	4,6	91	*m*-Chlorobenzoic acid	158
7	*p*-Chlorotoluene		162	2	38	*p*-Chlorobenzoic acid	242
8	*m*-Dichlorobenzene		172	4,6	103		
9	*o*-Dichlorobenzene		179	4,5	110		
10	*o*-Bromotoluene		181	3,5	82	*o*-Bromobenzoic acid	150 (147)
11	*m*-Bromotoluene		183	4,6	103	*m*-Bromobenzoic acid	155
12	*p*-Bromotoluene (*m* 26)		185	2	47	*p*-Bromobenzoic acid	251
13	*o*-Chloroanisole (see Table 11, compd. 36)		195				
14	*p*-Chloroanisole		200				
15	Iodobenzene		188	4	171	*p*-Bromoiodobenzene	91
16	2,4-Dichlorotoluene		195	3,5	104	2,4-Dichlorobenzoic acid	160
17	*m*-Iodotoluene	5	204			*m*-Iodobenzoic acid	186
18	*o*-Iodotoluene	5	211 (207)	6	103	*o*-Iodobenzoic acid	162
19	*p*-Iodotoluene (*m* 35)	5	211			*p*-Iodobenzoic acid	265 (270)
20	1,2,4-Trichlorobenzene		213	5	56		
21	*m*-Dibromobenzene		219	4	61		
22	*o*-Dibromobenzene		224	4,5	114		
23	2-Bromocymene		234		97	Anilide	143
24	3,4-Dibromotoluene		241			3,4-Dibromobenzoic acid	233
25	1-Chloronaphthalene (α-Chloronaphthalene)		263 (259)	4,5	180	Picrate	137
26	1-Bromonaphthalene (α-Bromonaphthalene)		281 (279)	4	85	Picrate Naphthalide	134 236
27	1-Iodonaphthalene (α-Iodonaphthalene)		305			Picrate	128

[a] Many "nitro aryl halides" are to be found in the table on nitro compounds (page 427). Phenacyl chloride, bromide, and substituted phenacyl halides will be found in the table of Ketones.

TABLE 26
Aromatic Halides (Solid)

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives: Recommended — Nitro: Position	Nitro: M. P. (°C)	Others: Name	Others: M. P. (°C)
1	2-Chlorobiphenyl		34			*o*-Chlorobenzoic acid	140
2	*p*-Iodotoluene		35			*p*-Iodobenzoic acid	265
3	1,2,3-Trichlorobenzene		52	4	56		
4	*p*-Dichlorobenzene (*b* 173)		53	2	54		
5	2-Iodonaphthalene		55v.s.			Anilide Picrate	170 95

TABLE 26—*Continued*
Aromatic Halides (Solid)

	Name of Compound	Note	M. P. (°C)	Melting Point of Derivatives — Recommended — Nitro — Position	M. P. (°C)	Others — Name	M. P. (°C)
6	2-Chloronaphthalene (*b* 265)		56 (61)	1,8	175	Picrate	81
7	2 Bromonaphthalene (*b* 281)		59			Picrate	79
8	1,3,5-Trichlorobenzene		63	2	68		
9	1,2-Dibromonaphthalene		67			3,4-Dibromophthalic acid	196
10	*p*-Bromochlorobenzene		67	2	72		
11	*p*-Nitrobenzyl bromide (See Table of Nitro Compounds)		71				
12	1,4-Dibromonaphthalene		82			3,6-Dibromophthalic acid	135
13	*p*-Dibromobenzene (*b* 219)		89	2,5	84		
14	*p*-Diiodobenzene		129			*p*-Iodonitrobenzene	171.5*
15	1,2,4,5-Tetrabromobenzene		180	3	168		
16	Naphthalene tetrachloride		182			1,3-Dichloronaphthalene	61
17	Hexachlorobenzene (*b* 326)		229*s* (226)			Chloranil	290

TABLE 27
Dihalides and Polyhalides

	Name of Compound	Note	B. P. (°C)	Density	*n*	Melting Point of Derivatives (°C)
1	Methylene chloride		42	1.378 0/4	1.4237	β-Naphthyl ether, 133
2	Dichloroethylene		55	1.25		
3	1,1-Dichloroethane (Ethylidene chloride)		60	1.180 22/4	1.4166	Di-β-naphthyl ether, 200
4	Chloroform	3	61	1.504 12/4	1 4467	
5	2,2-Dichloropropane		70	1.093	1.4093	
6	1,1,1-Trichloroethane (Methyl chloroform)		76 (74)	1.325 26/4	1.4349	
7	Carbon tetrachloride		78	1.667 16/4		
8	Ethylene chloride		83	1.256	1.4443	
9	Trichloroethylene		90	1.440 15/0	1.4782	
10	Methylene bromide		98	2.498 15/4		
11	Propylene chloride		98	1.166 14/4	1.4388	
12	1,1-Dibromoethane (Ethylidene bromide)		112	2.100 17/4	1.5128	
13	1,1,2-Trichloroethane		114	1.457		
14	Tetrachloroethylene		121	1.631 9/4	1.5055	
15	Trimethylene chloride		125 (122)	1.190 18/4 (1.180)		
16	Ethylene bromide		130	2.178	1.5379	Alkyl-isothiourea picrate, 260
17	Propylene bromide		142	1.933	1.5203	
18	*s*-Tetrachloroethane		147	1.614 0/4	1.4942	
19	Bromoform	6	151	2.904 15/4	1.589	
20	1,2,3-Trichloropropane		155	1.417		
21	Pentachloroethane		161	1.693 10/4	1.504	
22	Trimethylene bromide		165	1.973 17/4	1.523	
23	Methylene iodide		180*d*	3.285 15/4	1.7425	
24	Benzal chloride	7	212	1.295 16/4	1.5515	
25	1,2,3-Tribromopropane		219	2.436 23/4	1 584	

TABLE 27—*Continued*

Dihalides and Polyhalides

	Name of Compound	Note	B. P. (°C)	Density	n	Melting Point of Derivatives (°C)
26	Benzotrichloride		220 (218)	1.380 14/4	1.5573	Benzoic acid, 121.7
27	Ethylene iodide		*m.p.* 81			
28	1,1,1-Trichloro-2,2-bis (*p*-chlorophenyl) ethane (D.D.T.)	8	*m.p.* 108			
29	Iodoform	9	*m.p.* 119			
30	Hexachloroethane		*m.p.* 187*s*			

Notes on Halides

1. Forms quaternary salt with dimethylaniline, M. P. 110.
2. On oxidation gives *p*-chlorobenzoic acid, M. P. 242.
3. On oxidation gives *p*-bromobenzoic acid, M. P. 251.
4. Compound (200 mg) boiled with water (2 ml) for 5 minutes gives triphenylmethanol, M. P. 162.
5. Oxidizes with nitric acid if heated at 200° for 3 hours; resistant to permanganate oxidation.
6. Gives carbylamine test with aniline or any RNH_2.
7. Compound (200 mg) heated to 50° in 1 ml conc. H_2SO_4 for 5 minutes, diluted, neutralized, and treated with semicarbazide, as directed on page 246, gives benzaldehyde semicarbazone.
8. Impure product melts as low as 90° due to the presence of isomers. Pure commercial product melts at 108. For ident. see *J. Am. Chem. Soc.*, 66, 2129.
9. Characteristic odor; reduces with Na_3AsO_3 to CH_2I_2; forms compound with quinoline, M. P. 65*d*.

TABLE 28
Nitro Compounds

	Name of Compound	B. P. (°C)	Melting Point of Derivatives (°C)		
			Benzenesulfonamide[a]	Benzamide[a]	Others
	Liquids				
1	Nitromethane	101	30		See Table 18, compd. 1
2	Chloropicrin	113			
3	Nitroethane	114	58	71	
4	2-Nitropropane	121			See Table 18, compd. 4
5	1-Nitropropane	130	36	84	
6	1-Nitroisobutane	140.5	53	57	
7	1-Nitrobutane	152			See Table 18, compd. 10
8	Nitrobenzene	209	112	160	*m*-Dinitrobenzene, 90
9	*o*-Nitrotoluene	224	124	143	2,4-Dinitrotoluene, 70
10	*o*-Nitroethylbenzene	224		147	
11	2-Nitro-*m*-xylene (*m.p.* 13)	225_{744mm}			2,4,6-Trinitro-*m*-xylene, 182
12	Phenylnitromethane	226*d*	88	105	
13	*m*-Nitrotoluene (*m.p.* 16)	231 (227)	95	125	*m*-Nitrobenzoic acid, 140
14	2-Nitro-*p*-xylene	239_{759mm}	138	140	2,3,5-Trinitro-*p*-xylene, 139
15	*p*-Nitroethylbenzene	241		151	Trinitroethylbenzene, 37
16	4-Nitro-*m*-xylene (*m.p.* 2)	244_{744mm}			2,4,6-Trinitro-*m*-xylene, 182
17	3-Nitro-*o*-xylene (*m.p.* 15)	250			3,4-Dinitro-*o*-xylene, 82
18	2-Nitrocymene	264		102	2,6-Dinitrocymene, 54
19	*o*-Nitroanisole (*m.p.* 10)	265 (272)	89		2,4,6-Trinitroanisole, 68
20	*o*-Nitrophenetole	268	102		2,4-Dinitrophenetole, 86
	Solids	M. P. (°C)			
21	*m*-Nitrobenzyl alcohol	27			*m*-Nitrobenzoic acid, 140
22	4-Nitro-*o*-xylene	30			3,4-Dinitro-*o*-xylene, 82
23	*o*-Chloronitrobenzene	32	129	99	2,4-Dinitrochlorobenzene, 52(50)
24	2-Nitrobiphenyl	37(33)		102	
25	*m*-Nitroiodobenzene	38(35)			
26	Ethyl *m*-nitrobenzoate	41			
27	*o*-Bromonitrobenzene	43		116	2,4-Dinitrobromobenzene, 72
28	*m*-Chloronitrobenzene	44(45)	121	120	3,4-Dinitrochlorobenzene, 72
29	Nitromesitylene	44		204	Dinitromesitylene, 86
30	*o*-Iodonitrobenzene	49			*o*-Iodoaniline, 56
31	*p*-Nitrotoluene	51.9 (54)	120	158	2,4-Dinitrotoluene, 70
32	2,4-Dinitrochlorobenzene	52(50)		178	2,4-Dinitrophenol, 114
33	2,5-Dichloronitrobenzene	54		120	2,5-Dichloro-1,3-dinitrobenzene, 104
34	*p*-Nitroanisole	54(52)	95	154	2,4-Dinitroanisole, 89
35	*m*-Bromonitrobenzene	54(56)		136(120)	3,4-Dinitrobromobenzene, 59
36	4-Iodo-3-nitrotoluene	55			4-Iodo-3-aminotoluene, 38
37	3-Nitro-*p*-iodotoluene	55			
38	Ethyl-*p*-nitrobenzoate	56			Ethyl-*p*-aminobenzoate, 90
39	*p*-Nitrophenetole	60(58)	143	173	2,4-Dinitrophenetole, 86
40	3-Nitrobiphenyl	61(59)			
41	4-Iodo-2-nitrotoluene	61			4-Iodo-2-aminotoluene, 48
42	1-Nitronaphthalene (also α-)	61(57)	167	160	
43	*m*-Nitrobenzal chloride	65			*m*-Nitrobenzaldehyde, 58
44	2,6-Dinitrotoluene	66			2,4,6-Trinitrotoluene, 82
45	2,4,6-Trinitroanisole	68			Picric acid, 122.5
46	2,4-Dinitrotoluene	70(72)			2,4,6-Trinitrotoluene, 82; compd. with $C_{10}H_8$, 60; Acetyl-2,4-diaminotoluene, 224
47	*p*-Nitrobenzyl chloride	71			*p*-Toluidine, 45; *p*-Nitrobenzoic acid, 241; (See esters with alcohols, Table 5)
48	2-Nitro-*p*-chlorobromobenzene	72			
49	2,4,6-Trinitro-*o*-xylene	72(68)			
50	2,4-Dinitrobromobenzene	72			2,4-Dinitrophenol, 114

[a] The substituted amides refer to the derivatives of the amines formed by reduction of the nitro compounds.

TABLE 28—*Continued*

Nitro Compounds

	Name of Compound	M. P. (°C)	Melting Point of Derivatives (°C)		
			Benzene-sulfon-amide	Benz-amide	Others
51	*o*-Nitrobenzyl alcohol	74			Acetate, 35
52	3,5-Dinitro-*o*-xylene	76			
53	2-Nitronaphthalene (also β)	78	136	162	
54	2,4,6-Trinitrophenetole	78			Picric acid, 122.5
55	3,4-Dinitro-*o*-xylene	82			
56	*p*-Nitrobenzal chloride	82			
57	2,4,6-Trinitrotoluene	82			2,4,6-Trinitrobenzoic acid, compd. with $C_{10}H_8$, 97
58	3,5-Dinitrotoluene	82			
59	*p*-Chloronitrobenzene	83	121	192	*p*-Nitrophenol, 114
60	Picryl chloride	83	211		Picric acid, 122.5
61	2,5-Dinitro-*p*-dibromobenzene	84			
62	2,4-Dinitro-*m*-xylene	84(82)			
63	4-Bromo-1-nitronaphthalene	85			
64	4-Chloro-1-nitronaphthalene	87(85)			
65	2,4-Dinitroanisole	89(95)			2,4-Dinitrophenol, 114
66	*m*-Dinitrobenzene	90v s	194	240	*m*-Nitroaniline, 114 compd with $C_{10}H_8$, 52
67	2,4,5-Trinitro-*m*-xylene	90			
68	3,6-Dinitro-*o*-xylene	90			
69	2,3-Dinitro-*p*-xylene	93			
70	4,6-Dinitro-*m*-xylene	93			4,5,6-Trinitro-*m*-xylene, 125
71	2,4-Dinitrobiphenyl	93			
72	*p*-Nitrobenzyl alcohol	93			Acetate, 78
73	8-Chloro-1-nitronaphthalene	94			
74	*p*-Nitrobenzyl bromide	99			See esters with alcohols, Table 5
75	8-Bromo-1-nitronaphthalene	99-100			
76	2,5-Dinitro-*m*-xylene	101			
77	2,3′-Dinitrobiphenyl	110			
78	5-Chloro-1-nitronaphthalene	111			
79	4-Nitrobiphenyl	114		230	Acetamide, 171
80	3,4,5-Trinitro-*o*-xylene	115			
81	*o*-Dinitrobenzene	118	186	301	*o*-Nitroaniline, 71
82	4,5-Dinitro-*o*-xylene	118(115)			
83	1,3,5-Trinitrobenzene	122			Compd. with anthracene, 164
84	5-Bromo-1-nitronaphthalene	122.5			
85	Trinitrophenol (Picric acid)	122.5			Acetate, 76
86	2,6-Dinitro-*p*-xylene	123			
87	4,5,6-Trinitro-*m*-xylene	125			
88	*p*-Bromonitrobenzene	126	134	204	*p*-Nitrophenol, 114
89	2,2′-Dinitrobiphenyl	128(124)			
90	4,5-Dinitro-*m*-xylene	132			
91	4-Chloro-1,5-dinitronaphthalene	138			
92	2,3,5-Trinitro-*p*-xylene	139(137)			
93	4-Bromo-1,5-dinitronaphthalene	143			
94	4-Chloro-1,3-dinitronaphthalene	146.5			
95	2,5-Dinitro-*p*-xylene	147			
96	1,4,5-Trinitronaphthalene	154			
97	Picramic acid	169		230(220)	See Table 42
98	1,8-Dinitronaphthalene	170			1,3,8-Trinitronaphthalene, 218
99	4-Bromo-1,8-dinitronaphthalene	170			
100	6-Nitro-3,4,7-trimethylcoumarin	170			
101	*p*-Nitroiodobenzene	171(173)		222	*p*-iodoaniline, 62
102	*p*-Dinitrobenzene	173(171)	247	300	*p*-Nitrophenol, 114
103	4-Chloro-1,8-dinitronaphthalene	180			
104	2,4,6-Trinitro-*m*-xylene	182-3			
105	3,3′-Dinitrobiphenyl	200			
106	1,5-Dinitronaphthalene	214			1,4,5-Trinitronaphthalene, 154
107	1,3,8-Trinitronaphthalene	218			
108	4,4′-Dinitrobiphenyl	237 (229; 240)			

TABLE 29

Nitroso, Azoxy, Hydrazo, and Azo Compounds

	Name of Compound	M. P. (°C)	Melting Point of Derivatives (°C)
	Nitroso Compounds		
1	p-Nitrosotoluene	48	p-Toluidine, 45
2	m-Nitrosotoluene	53	with p-$BrC_6H_4NH_2$, 152
3	N-Nitrosodiphenylamine	66	Diphenylamine, 54
4	Nitrosobenzene	68	with $C_6H_5NH_2$, 68 with p-$BrC_6H_4NH_2$, 88
5	o-Nitrosotoluene	72	with p-$BrC_6N_4NH_8$, 82
6	p-Nitroso-N,N-diethylaniline	84	
7	p-Nitroso-N,N-dimethylaniline	85 (87)	
8	α-Nitrosonaphthalene	98	α-Naphthylamine, 50
9	1-Nitroso-2-naphthol	109	
10	p-Nitrosophenol	125*d*	p-Aminophenol, 184*d*
11	p-Nitrosodiphenylamine	144	
12	2-Nitroso-1-naphthol	152*d*	
13	Nitrosothymol	162	
	Azoxy Compounds		
14	Azoxybenzene	36	Azobenzene, 68
15	m-Azoxytoluene	39	m-Azotoluene, 55
16	o-Azoxytoluene	60	o-Azotoluene, 55
17	p-Azoxytoluene	70	p,p'-Hydrazotoluene, 134
18	o-Azoxyanisole	81	
19	p-Azoxyanisole	119	
20	p-Azoxychlorobenzene	154	
	Hydrazo Compounds		
21	o-Hydrazoanisole	102	
22	Hydrazobenzene	130	Azobenzene, 68
23	p-Hydrazotoluene	134	p-Azotoluene, 144
24	2,2′-Hydrazonaphthalene	140	
25	1,1′-Hydrazonaphthalene	153	
26	o-Hydrazotoluene	165	o-Azotoluene, 55
	Azo Compounds		
27	o-Azotoluene	55	o-Hydrazotoluene, 165
28	m-Azotoluene	55	
29	Azobenzene	68	Hydrazobenzene, 130
30	Benzeneazodiphenylamine	96	
31	p-Dimethylaminoazobenzene	117	
32	p-Aminoazobenzene	127.4	See Table 42
33	o-Azophenetole	131	
34	p-Azotoluene	144	p-Hydrazotoluene, 134
35	p-Hydroxyazobenzene	152	
36	p-Azophenetole	160	
37	1,1′-Azonaphthalene	190	

TABLE 30
Nitriles (Liquid and Solid)

	Name of Compound	B. P. (°C)	Carboxylic acid formed by hydrolysis M. P. (°C)	Melting Point of Derivatives (°C)		
				Semicarbazone from ketone, C_6H_5COR	Alkyl 2,4,6 Trihydroxyphenyl-ketone	α-Iminoalkyl-mercaptoacetic acid hydrochloride
	Liquid Nitriles					
1	Acrylonitrile	78	*b.p.* 140			
2	Acetonitrile	81	*b.p.* 118	199	218	114
3	Propionitrile	97	*b.p.* 141	174	175	124
4	Isobutyronitrile	108	*b.p.* 155			
5	Butyronitrile	118	*b.p.* 165	184	181	135
6	Allyl cyanide (β-Butenonitrile)	118	*b.p.* 169			
7	Isovaleronitrile	130	*b.p.* 176			133
8	Valeronitrile	141	*b.p.* 186	157	149	137
9	Furonitrile	147	*m.p.* 133			
10	Isocapronitrile	155	*b.p.* 200	146	122	128
11	*n*-Captronitrile	164	*b.p.* 205	128	121	136
12	Oenanthonitrile (Heptanonitrile)	186	*b.p.* 223			133
13	Benzonitrile	190.2 (189)	*m.p.* 121.7			124
14	Caprylonitrile	200	*b.p.* 239			134
15	*o*-Tolunitrile	205	*m.p.* 104			
16	*m*-Tolunitrile	212	*m.p.* 110			168
17	*p*-Tolunitrile	217	*m.p.* 178			181
18	Phenylacetonitrile	234	*m.p.* 76.5			144
19	γ-Hydroxybutyronitrile	240	*b.p.* 204[a]			
20	Decanonitrile	245	*m.p.* 31			
21	Cinnamonitrile	254	*m.p.* 133			
22	Dodecanonitrile	280	*m.p.* 42			
23	Glutaronitrile	286	*m.p.* 98			
	Solid Nitriles	M. P. (°C)				
24	Tetradecanonitrile	19.5	54			
25	Hexadecanonitrile	31.5	63			
26	Heptadecanonitrile	34	61			
27	α-Naphtonitrile	35 (32)	162			
28	Octadecanonitrile	41	70			
29	Succinonitrile	54 (49)	185			
30	β-Naphthonitrile	66 (62)	184			
31	*p*-Chlorobenzonitrile	92	242			
32	*p*-Bromobenzonitrile	112	251			
33	*p*-Nitrophenylacetonitrile	116	153			
34	*m*-Nitrobenzonitrile	118	140			
35	Methylaminoacetonitrile	129	232*d*			
36	*p*-Nitrobenzonitrile	147	241			

[a] *b.p.* of lactone.

TABLE 31

Isocyanides, Isocyanates, and Isothiocyanates[a]

	NAME OF COMPOUND	B. P. (°C)	MELTING POINT OF DERIVATIVES (°C)
1	Methyl isocyanate	43-45	Isocyanates boiled with aqueous alkali yield the corresponding amines, which can be derivatized. For derivatives of phenylisocyanate and α-naphthylisocyanate, see the corresponding urethans from alcohols. Isocyanides treated with concentrated mineral acids yield corresponding amines at room temperature. Isothiocyanates yield thioureas with amines.
2	Methyl isocyanide	59.6	
3	Ethyl isocyanate	60	
4	Isopropyl isocyanate	67	
5	Ethyl isocyanide	78-9	
6	Isopropyl isocyanide	87	
7	Phenyl isocyanide	165-6	
8	Phenyl isocyanate	166	With $(CH_3)_2CHCH_2OH$ → deriv., *m*86
9	*o*-Tolyl isocyanide	183-4	
10	*o*-Tolyl isocyanate	186	
11	*p*-Tolyl isocyanate	187	
12	Phenyl isothiocyanate	220	With $C_6H_5NH_2$ → deriv., *m*153
13	*o*-Tolyl isothiocyanate	239	With $C_6H_5NH_2$ → deriv., *m*139
14	*p*-Tolyl isothiocyanate	239	With $C_6H_5NH_2$ → deriv., *m*141
15	α-Naphthyl isocyanate	269-270	With CH_3OH → deriv., *m*124
		M. P. (°C)	
16	*p*-Chlorophenyl isothiocyanate	45	With $C_2H_5NH_2$ → deriv., *m*154
17	α-Naphthyl isothiocyanate	58 (53)	With $C_2H_5NH_2$ → deriv., *m*158
18	*m*-Nitrophenyl isothiocyanate	60.5	With $C_2H_5NH_2$ → deriv., *m*155
19	β-Naphthyl isothiocyanate	62-3	With $C_2H_5NH_2$ → deriv., *m*182

[a] *Isocyanides* are also called *carbylamines:* methylcabylamine, phenylcarbylamine, etc.; *isocyanates* are also called *carbonimides: phenylcarbonimide* and *ethylcarbonimide.* **All isocyanides and isocyanates have intense and nauseating odors, are irritating to the mucous membranes, and often have severe toxic and lacrymatory effects.**

TABLE 32

Carbohydrates[a]

	Name of Compound	Note	M. P. (°C)	$[\alpha]_D^{20°}$	Derivatives: Azoates M. P. (°C)	Derivatives: Azoates $[\alpha]^{25°}_{6438,CHCl_3}$
1	*β*-Melibiose dihydrate, $C_{12}H_{22}O_{11}+2H_2O$		82-85	+129 5	280	172
2	*D*-Ribose		95	−23 7 (−21.5)		
3	*β* Maltose hydrate, $C_{12}H_{22}O_{11}+H_2O$	1	102 5	+136	275	+2
4	*β*-*D*-Fructose		102 4(A)	−92.0	125	−440
5	Raffinose	2	119	+123.1	145	+146
6	*β*-*L*-Rhamnose	3	122-6(Ac)	+9.1		
7	*D*-Mannose	4	133	+14.5		
8	*D*-Xylose	5	143*	+19.1 (W4½)	157	+244
9	*α*-*L*-Fucose		145	−75.9		
10	*α*-*D*-Glucose		146	+52.7	266	+223
11	Melezitose dihydrate		155	+88.8	130 (sinters)	+188
12	*L*-Sorbose		159-60	−43.1		
13	*β*-*D*-Galacturonic acid		160	+55.3		
14	*β*-*L*-Arabinose		160	+104.5	262	+755

[a] Special symbols used in this table:

(A) = ethyl alcohol as solvent
(W) = water as solvent
(P) = pyridine as solvent
(P-A) = 50-50 pyridine-alcohol as solvent
(M) = methyl alcohol as solvent
(Aa) = acetic acid as solvent
(Ac) = acetone as solvent

Where a letter followed by a number appears within parentheses, the letter stands for the solvent and the number signifies the number of hours required to attain equilibrium in mutarotation. Thus, for the phenylhydrazone of *D*-Mannose, +33.8 (P 56) means that pyridine is used as a solvent and that equilibrium is attained in 56 hours. The initial value, not given in the table, is $[\alpha]_D = +26.3$. This value changes to −6.3° in 9 hours. After 56 hours it again becomes positive and attains a state of equilibrium with a value of $[\alpha]_D = +33.8$; which is the recorded value.

Where the solvent (for rotation or crystallization) is water, the (W) is omitted, unless admixed with alcohol or where for some special reason it is deemed best to specify it.

TABLE 32—*Continued*
Carbohydrates

Derivatives—(*Continued*)

Others

		M. P. (°C)	$[\alpha]_D^{20°}$
1	Phenylosazone	176-8	+43.2(P)
2	*p*-Bromophenylhydrazone	170*	−5.7(A)
	Dimethylmethane dimethyldihydrazone	141-2	
3	Phenylosazone	208	
	Semicarbazone	213*d*	+80(W)
	β-Naphthylhydrazone	176	+10.6(M)
	Octaacetate	158	
4	*p*-Nitrophenylhydrazone	180-1 (176)	+16(P-A)
	o-Nitrophenylhydrazone	156-7*	+31(P-A)
	α-Methylphenylosazone	161-2*	+83.5(P-A)
	Phenylosazone	210	
5	α-Methylphenylhydrazone	190*	
6	*p*-Nitrophenylhydrazone	190-1	+21.4
	α-Methylphenylhydrazone	124	
	Phenylosazone	222 (185)	+94(P)
	p-Bromophenylosazone	222	
7	Phenylosazone (Glucosazone)	210	
	Phenylhydrazone	199	+33.8(P 56)
	Methylphenylhydrazone	181	+8.6(M)
	p-Bromophenylhydrazone	208	
	p-Nitrophenylhydrazone	195(A) (203)	+56.0(P-A)
8	*m*-Nitrophenylhydrazone	163(A)	
	Phenylosazone	164*(A-W)	
	Phenylosotriazole	89*	
	β-Naphthylhydrazone	124*	
9	*p*-Bromophenylhydrazone	181-4(A-W)	
	p-Toluene sulfonylhydrazone	174	−17.0(P)
	Phenylhydrazone	170	
	p-Nitrophenylhydrazone	210-1	
10	Phenylosazone	210(211W)	−1.5(P-A)
	p-Nitrophenylhydrazone	190(196)	+21.5(P-M)
	β-Naphthylhydrazone	178*	+11(A)
	Phenylosotriazole	195-6*	−81.6(P)
	α-Pentaacetate	112	
	β-Pentaacetate	132	
11			
12	*p*-Bromophenylosazone	181	
	Phenylosotriazole	159*	
13	*p*-Bromophenylhydrazone	151*d*	+11.5(M)
14	Phenylosazone	166	
	Cinchonine salt	178	+139(W)
	Benzylphenylhydrazone	174*	−11.5(M)
	Methylphenylhydrazone	165*	
	Diphenylhydrazone	204-5*	+14.9(P)
	Phenylhydrazone	153	+7.95(P)
	p-Nitrophenylhydrazone	186(W)	
	β-Naphthylphenylhydrazone	177(A)	
	Semicarbazone	190	+23.8(W)
	Oxime	139	+13.3(W)

TABLE 32—*Continued*

Carbohydrates

	Name of Compound	Note	M. P. (°C)	$[\alpha]_D^{20°}$	Derivatives: Azoates M. P. (°C)	Derivatives: Azoates $[\alpha]^{25°}_{6438, CHCl_3}$
15	*α-D*-Galactose		165.5*	+81.7	276	+436
16	*β-D*-Glucuronic acid		165*	+36.3		
17	*β*-Inulin			−40		
18	Sucrose	6	185	+66.5	125	+35
19	*α*-Lactose monohydrate		202	+52.3		
20	*α,α*-Trehalose		203	+197.1	134.5	+210
21	*α*-Lactose (anh.)		223		288	+320
22	*β*-Lactose (anh.)		252	+53.6		
23	Cellobiose		225	+35.2	273	105
24	Starch (sol.)		dec.	+189		
25	Glycogen		240*d*			

Notes on Carbohydrates

1. According to the literature maltose when carefully heated to 160° C. (in vacuo) loses water, and is resolved into the anhydride maltosan ($C_{12}H_{20}O_{10}$), a brown amorphous powder, which does not regenerate maltose when boiled with water and melts at 145–50. *β*-Maltose hydrate is stated to melt at 160–5 and at 102–3; the anhydrous form at 108. Beilstein (XXI, 386) gives the following melting points for hydrate: 110–125*d*, 106–112, 115, 115–125, 125–30; for the anhydrous form it gives no melting point but only the temp. of dehydration.

2. Raffinose crystallizes with five molecules of water and is freed therefrom by very slow heating.

3. *α-L*-Rhamnose crystallizes with one molecule of water, and by cautious heating for several days is converted into anhydrous *β-L*-rhamnose, which can be recrystallized from acetone.

4. *D*-Mannose does not occur in nature as such, but only in the form of the polymerized anhydride *mannan*, from which it may be obtained by hydrolysis. It can be made by oxidation of *d*-mannitol.

5. *D*-Xylose, formerly called *l*-xylose, is best identified microscopically by conversion into "Cd xylonobromide,"[2] $Cd(C_5H_9O_6)_2 \cdot CdBr_2 \cdot 2H_2O$, by means of Br_2 and $CdCO_3$. (Bertrand, *Bull. soc. chim.* (3) **5**, 556; **7**, 501; **15**, 592; cf. Widtsoe, *Ber.* **33**, 136); or as the brucine salt of *d*-xylonic acid (Neuberg, *Ber.* **35**, 1470–3).

6. Sucrose when crystallized from methyl alcohol melts 169–70, from ethyl alcohol *m* 179–80, from ethyl alcohol and water *m* 184–5. (Heldermann, *Z. physik. chem.*, **130**, 396 (1927) and Pictet and Vogel, *Helv. Chim. Acta*, **11**, 436 (1928).

TABLE 32—*Continued*
Carbohydrates

	Derivatives—(*Continued*)		
	Others (*Continued*)		
		M. P (°C)	$[\alpha]_D^{20°}$
15	*o*-Tolylhydrazone	176*(95% A)	
	m-Tolylhydrazone	154*	
	α-Methylphenylhydrazone	190-1*	inactive
	p-Nitrophenylhydrazone	197(W)*	+45 6
	Phenylosazone	182-4; 201	+0.34(PA-24)
	Phenylosotriazole	111*	
	Mucic acid	214*d*	
	α-Pentaacetate	95	
	β-Pentaacetate	142	
16	Cinchonine salt	204*	+139 9(W)
	p-Nitrophenylhydrazone	225	
	Semicarbazone	188	
	Thiosemicarbazone	223	
17	Triacetate	150-60	−45.5(Ac)
18	Octaacetate	75(69)	+59.6($CHCl_3$)
	Tritrityl	127-9	+44.3
19	Phenylosazone	210(200)	+7.9(M9)
	p-Nitrophenylosazone	258	
	Phenylosotriazole	181*	
	Mucic acid	214*d*	
	Octaacetate	100	
20	Octaacetate	100-2*	+162($CHCl_3$)
21			
22			
23	Octaacetate	229.5	+42.0($CHCl_3$)
	Semicarbazone	183-5	−5.2(W)
	Thiosemicarbazone	170*d*	
	Phenylosazone	200*d*	−6.5(P-A)
	Phenylosotriazole	165*	
24			
25	Triacetate		+170($CHCl_3$)
	Dibenzoate		+179.8($CHCl_3$)

TABLE 33

Hydrocarbons (Paraffins and Cycloparaffins)

	Name of Compound	B. P. (°C)	Density$_4^{20}$	n_D^{20}
1	Neopentane	9	0.613	1.3513
2	Isopentane (2-Methylbutane)	28	0.620	1.3580
3	Pentane	36	0.626	1.3577
4	Cyclopentane	49	0.746	1.4068
5	2,2-Dimethylbutane	49	0.649	1.3689
6	2,3-Dimethylbutane	58	0.662	1.3750
7	2-Methylpentane	60	0.653	1.3716
8	3-Methylpentane	63	0.664	1.3764
9	Hexane	69	0.659	1.3751
10	Methylcyclopentane	72	0.749	1.4100
11	2,2-Dimethylpentane	79	0.674	1.3823
12	2,4-Dimethylpentane	80	0.673	1.3823
13	Cyclohexane	81	0.778	1.4264
14	2,2,3-Trimethylbutane	81	0.690	1.3894
15	3,3-Dimethylpentane	86	0.693	1.3911
16	2,3-Dimethylpentane	89	0.695	1.3920
17	2-Methylhexane	90	0.679	1.3851
18	3-Methylhexane	92	0.687	1.3887
19	Heptane	98	0.684	1.3877
20	2,2,4-Trimethylpentane	99	0.692	1.3916
21	Methylcyclohexane	100	0.769	1.4231
22	2,2-Dimethylhexane	107	0.695	1.3930
23	2,5-Dimethylhexane	109	0.694	1.3930
24	2,2,3-Trimethylpentane	110	0.717	1.4030
25	3,3-Dimethylhexane	112	0.708	1.3992
26	2,3,3-Trimethylpentane	113	0.726	1.4074
27	2,3-Dimethylhexane	115	0.712	1.4015
28	3,4-Dimethylhexane	117	0.720	1.4044
29	4-Methylheptane	118	0.717	1.3981
30	3-Methylheptane	119	0.710	1.3988
31	1,4-Dimethylcyclohexane (*trans*)	119	0.763	---
32	1,3-Dimethylcyclohexane (*trans*)	120	0.766	---
33	2,2,4,4-Tetramethylpentane	122	0.718	1.4070
34	1,2-Dimethylcyclohexane (*trans*)	123	0.766	---
35	1,4-Dimethylcyclohexane (*cis*)	124	0.783	---
36	1,3-Dimethylcyclohexane (*cis*)	125	0.783	---
37	Octane	125	0.703	1.3976
38	1,2-Dimethycyclohexane (*cis*)	130	0.796	---
39	Ethylcyclohexane	132	0.788	1.4332
40	2,6-Dimethylheptane	135	0.709	1.4007
41	3,3-Dimethylheptane	138	0.730	1.4095
42	2-Methyloctane	143	0.713	1.4032
43	Nonane	150	0.718	1.4056
44	Isopropylcyclohexane	154	0.802	1.4410
45	*n*-Propylcyclohexane	155	0.793	1.4370
46	2,7-Dimethyloctane	160	0.735	1.4080
47	*p*-Menthane	169	0.796	1.4369
48	Decane	174	0.730	1.4120
49	*n*-Butylcyclohexane	180	0.800	1.4408
50	Decahydronaphthalene (*trans*) (Decalin)	185	0.870	1.4697
51	Isoamylcyclohexane	193	0.802	1.4423
52	Decahydronaphthalene (*cis*) (Decalin)	194	0.896	1.4811
53	Undecane	196	0.740	1.4190
54	Dodecane	216	0.749	1.4218
55	Tetradecane	251	0.764	1.4360
56	Pentadecane (*m.p.* 10)	268	0.769	1.4310
57	Hexadecane (Cetane, *m.p.* 18)	280	0.775	1.4352
58	Octadecane (*m.p.* 28; 30)	177/15mm	0.782	(43°)1.434
59	Eicosane (*m.p.* 36.7; 38)	205/15mm	0.788	(32°)1.4344

TABLE 34
Unsaturated Hydrocarbons

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density$_4^{20}$	n_D^{20}	Melting Point of Derivatives (°C)	
							Bromo	Others
1	1,3-Butadiene		−108.9	−4.54	.6206	1.4292^{25}		α-Naphthoquinone, 105-6 (*Ann. 460*, 98)
2	1-Butyne		−122.5	+8.6	.6784	1.3962		K_2HgI_4→ dibutynyl Hg, 162-3
3	3-Methyl-1-butene (pol.)		−180	20.2	$.6320_{25}^{15}$	1.3675_{25}^{15}	liq.	
4	2-Butyne		−32.2	27.2	.688	1.3893	243 (tetra)	
5	3-Methyl-1-butyne			28	.666	1.3785	liq.	
6	1-Pentene (amylene)		138	30.1	.6410	1.3710	liq.	
7	Furan		−85.6	31.3	.9366	1.42157		Maleic anh. → 3,6-endoxo-Δ^4-tetrahydrophthalic anh., 125*d*
8	Isoprene (2-Methyl-1,3-butadiene) (pol.)		−146.8	34.1	.6805	1.4216	liq.	Thiocyanate, 77; maleic anh. → tetrahydro-4-methylphthalic anh., 64
9	*trans*-2-Pentene		−135.5	36.25	.6486	1.3790	liq.	
10	*cis*-2-Pentene		−179	37.0	.6562	1.3822	liq.	
11	2-Methyl-2-butene		−123	38.4	.6620	1.3878	non-homog.	Amyl nitrite → nitrosochloride, 74
12	1-Pentyne		−98	39.7	.6945	1.3847	liq.	K_2HgI_4 → dipentynyl Hg, 118.5
13	1,3-Cyclopentadiene (pol.)		−85	41.0	.7983	1.4461	liq.	Dimer, 32 (*b* 170); + benzoquinone, 76; maleic anh. → *cis*-3,6-Endomethylene-Δ^4-tetrahydrophthalic anh., 164.
14	Piperylene (1,3-pentadiene)		−88.9	42.3	.6803	1.4309	114 (tetra)	Maleic anh. → 3-methyl-1,2,3,6-tetrahydrophthalic anh., 61-2
15	Cyclopentene		−134.6	44.2	.7736	1.4225	liq.	N_2O_3 → pseudonitrosite, 70
16	1-Hexene		−141	63.15	.6734	1.38758	liq.	
17	2,3-Dimethyl-1,3-butadiene (pol.)		−76	68	.7263	1.4390	138 (tetra)	
18	2,3-Dimethyl-2-butene (tetramethylethylene)		−76.4	73	.7081	1.41153		
19	1,3-Cyclohexadiene (1,2-Dihydrobenzene)	1	−104.8	80.3	.8413	1.4740	vary	Maleic anh. → 3,6-endoethylene-1,2,3,6-tetrahydrophthalic anh., 147; α-Naphthoquinone, 135
20	2,4-Hexadiene (Dipropenyl)		−79	81	.7152	1.4493	185 (tetra)	Maleic anh. → 2,5-Dimethyl-1,2,5,6-tetrahydrophthalic anh., 95
21	Cyclohexene		−103.4	83	.8088	1.44646	liq.	Nitrosochloride, 153*d*; 1,2-dithiocyanate, 58; $KMnO_4$ → adipic acid, 154
22	1-Heptene		−120	92.8	.6971	1.3998	liq.	
23	1-Heptyne		−81	100	.7338	1.4084	vary	K_2HgI_4 → $(C_5H_{11}C{\equiv}C)_2Hg$, 61
24	2,4,4-Trimethyl-1-pentene ('Diisobutylene')		−93.6	101.2	.7151	1.4082		
25	Cycloheptene (Suberene)		−56	115*	.8228	1.4580		Nitrosochloride 118; oxidation with HNO_3 gives pimelic acid, 105.
26	1-Octene		−104	122	.7155	1.4088		
27	1-Octyne		−80	126	.7470	1.4172		K_2HgI_4 → $(C_6H_{13}C{\equiv}C)_2Hg$, 80.5
28	Ethynylbenzene (Phenylacetylene)		−40	141.7	.9281	1.5485	liq.	
29	Styrene (pol.)		−30.6	145.2	.9056	1.5470	74 (di) (77) (71)	Dithiocyanate, 103

TABLE 34—*Continued*

Unsaturated Hydrocarbons

	Name of Compound	Note	M. P. (°C)	B. P. (°C)	Density$_4^{20}$	n_D^{20}	Melting Point of Derivatives (°C)	
							Bromo	Others
30	α-Pinene		−50	156	.8600	1.4560	169 (di)	Oxidation with $Hg(OAc)_2$ → sobrerol, *m* 150, and 8-hydroxycarvotanacetone (semicarbazone, 176); oxidation with $KMnO_4$ at 30° in acid solution gives pinonic acid, 103-5 (semicarbazone, 205). Nitrolbenzylamine, 123; nitrolpiperidine, 119; nitrosochloride, 109; nitroso, 132.
31	Allylbenzene			157	.8912	1.5042[25]		
32	Myrcene			166-7	.7982	1.47065		Maleic anhydride addition, 33-4; dihydromyrcene tetrabromide, 96
33	*d*-Limonene		−95.5	176.7 (178)	.8446	1.4739	104 (tetra)	Dihydrochloride, 50; nitrosochloride, 100-4; nitrolbenzylamine, 92; nitroso, 72
34	Dipentene (*dl*-Limonene)			177-8	.8402	1.4727	124 (tetra)	Dihydrochloride, 50
35	Sylvestrene			180 (176)	.8479	1.4760	135 (tetra)	Dihydrochloride, 72; nitrosochloride, 107; nitrolbenzylamine, 71
36	Indene (pol.)		−2	181	.9915	1.5764	32 (di)	Bromohydrin, 128-9; picrate, 98 (very explosive); nitrosochloride, 150; nitrolamine, 157
37	1,4-Dihydronaphthalene		24	212	.998	1 5740		Nitrosochloride, 143-4; nitrolamine, 146
38	*l*-Camphene		51 3*	160-1	8555	1 46207		Hydrochloride, 125-7; H-phthalate, 163-4; *p*-Toluenesulfonic acid → isoborneol, 214
39	Stilbene		124	306 s	.970$_{13}^{126}$		237(α-di) 110(β-di)	Na + C_2H_5OH → bibenzyl, 52; nitrosite, 196*d* (α,α′-dinitrobenzyl, 236) picrate, 94-5; with 1,3,5-$C_6H_3(NO_2)_3$ gives compd. 120 (101)

TABLE 35

Aromatic Hydrocarbons (Liquid)

	Name of Compound	Note	B. P. (°C)	Density$_4^{20}$	Melting Point of Derivatives (°C)				
					Nitro		Aroyl-benzoic acid	Picrate[a]	Acetamino (Ac) or Diacetamino (Di)
					Position	M. P.			
1	Benzene		80	0.879	1,3	89	127	84u	
2	Toluene	2	111	0.867	2,4	70	137	88u	221(Di)
3	Ethylbenzene		136	0.876	2,4,6	37	122	96u	223(Di)
4	*p*-Xylene	3	136.4	0.861	2,3,5	139	132	90u	
5	*m*-Xylene	3	139.2	0.864	2,4,6	183	126	91u	
6	*o*-Xylene	3	144.5	0.880	4,5	118	178	88u	

[a] The letter "u" appearing after the melting point of the picrate indicates that the molecular compound is unstable, in that it cannot be purified with ease.

TABLE 35—*Continued*
Aromatic Hydrocarbons (Liquid)

	Name of Compound	Note	B. P. (°C)	Density$_4^{20}$	Melting Point of Derivatives (°C)				
					Nitro		Aroyl-benzoic acid	Picrate	Acetamino (Ac) or Diacetamino (Di)
					Position	M. P.			
7	Isopropylbenzene (Cumene)		152.4	0.8615	2,4,6	109	133		106(Ac) 216(Di)
8	*n*-Propylbenzene		159	0.862			125	103u	96(Ac) 208(Di)
9	Mesitylene		164.6	0.865	2,4	86	211	97u	
10	*tert*-Butylbenzene		168						170(Ac) (210Di)
11	Pseudocumene		169	0.876	3,5,6	185		97u	
12	*p*-Cymene		175	0.864	2,6	54	123		
13	Indene		182					98	
14	*m*-Diethylbenzene		182	0.860	2,4,6	62	114		
15	*n*-Butylbenzene		182	0.864			97		105(Ac) 214(Di)
16	*tert*-Amylbenzene		187						142(Ac) 181(Di)
17	*sec*-Amylbenzene		188						107(Ac)
18	Isodurene		198	0.8906	4,6	181 (157)	213		
19	*n*-Amylbenzene		205	0.858					101(Ac)
20	Tetralin		206	0.971	5,7	95	153		
21	Cyclohexylbenzene		237	0.955	4	58			
22	1-Methylnaphthalene		245	1.016	4	71		142	

TABLE 36
Aromatic Hydrocarbons (Solid)

	Name of Compound	Note	M. P. (°C)	Density$_4^{20}$	Melting Point of Derivatives (°C)			
					Nitro		Aroyl benzoic acid	Picrate
					Position	M. P.		
1	Diphenylmethane	4	25.3		2,4,2′,4′	172		
2	2-Methylnaphthalene		34.4		1	81		116
3	Pentamethylbenzene		51		6	154		131
4	Bibenzyl		53		4,4′	180		
5	Biphenyl		69.2 s; v.s.		4,4′	237 (229)	224	
6	Durene		79	0.838	3,6	205	263	
7	Naphthalene		80.8 s; v.s.	0.9752	1	61 (57)	172	149
8	Triphenylmethane		92		4,4′,4″	206		
9	Retene	5	95.2*s*					124
10	Acenaphthene	5	96.2*s*		5	101	198	161
11	Phenanthrene	5	96.3					144u
12	Fluorene	8	113.5		2,7	199	227	84
13	Pyrene (*b* 385)	8	148					
14	1,1′-Binaphthyl		160					145
15	Hexamethylbenzene		165					170
16	2,2′-Binaphthyl		188					184
17	Anthracene	6	216*s*					138u
18	Chrysene ($C_{18}H_{12}$) (*b* 448)	7	251					
19	Picene ($C_{22}H_{14}$) (*b* 520)	8	364					

1. 1,3-Cyclohexadiene with bromine in $CHCl_3$ or n-C_6H_{14} forms a dibromo compound with M.P. 68, but isomerizes rapidly to 1,4-dibromo-2-cyclohexene, M.P. 108, which adds no more bromine, but the isomer melting at 68, when treated with bromine, yields two tetrabromo derivatives, one form melting at 87–89 and the other at 155–6.

2. Toluene is oxidized readily to benzoic acid, M.P. 121.7.

3. The three xylenes are oxidized by $KMnO_4$ to dicarboxylic acids: *o*-xylene to phthalic; *m*-xylene to isophthalic and *p*-xylene to terephthalic acids.

4. Oxidized by HNO_3 to benzophenone.

5. Molecular compounds with trinitrobenzene: retene: *m* 139; acenaphthene: *m* 168; phenanthrene: *m* 145.

6. Oxidizes to anthraquinone; bromination in acetic acid gives dibromo derivative: *m* 122; trinitrobenzene molecular compound: *m* 164.

7. Dibromo derivative by bromination in acetic acid: *m* 275; trinitrobenzene molecular compound: *m* 190.

8. T.N.F. deriv.: fluorene: *m* 179; Pyrene: *m* 242; anthracene: *m* 194; chrycene: *m* 249; picene: *m* 257.

TABLE 37

Thiols,[a] or Mercaptans[b]

	Name of Compound	B. P. (°C)	M. P. (°C)	Melting Point of Derivatives (°C)				
				2,4-Dinitrophenyl thio ether	2,4-Dinitrophenyl sulfone	3,5-Dinitrothio benzoate	3-Nitrothiophthalate	Anthraquinone thio ether
1	Methyl	6		128*	189.5*			221
2	Ethyl	36		115	160	62	149	184
3	Isopropyl	56		94	140.5	84	145	
4	*n*-Propyl	67		81	127.5	52	137	151
5	Isobutyl	88		76	105.5	64	136	144
6	*n*-Butyl	97		66	92	49	144	
7	Isoamyl	117		59	95	43	145	86
8	*n*-Amyl	126		80	83	40	132	129
9	*n*-Hexyl	151		74	97			114
10	Thienyl	166		119	143			
11	Phenyl (Thiophenol)	169		121	161	149	131	
12	*n*-Heptyl	176		82	101	53	132	96
13	Benzyl	194		130	182.5	120	137	
14	*p*-Tolyl (*p*-Cresyl)	195	43	103	189.5			
15	*n*-Octyl	199		78	98			95
16	α-Phenylethyl	199		89	133.4			
17	*n*-Nonyl	220		86	92			117.5
18	Cetyl (Hexadecyl)		50.5	91				
19	Biphenyl		111	146	170			

[a] *Thiols* is the modern name now coming into use for *mercaptans*, thus, methanethiol, ethanethiol, etc.
[b] For extensive tables of thiols, thio ethers, sulfones, sulfonamides and sulfonic acids, see *Organic Chemistry of Sulfur*, Suter, John Wiley and Sons, Inc., New York (1944).

TABLE 38

Thioethers (Sulfides)

	Name of Compound	B. P. (°C)	Melting Point of Derivative (°C)		Name of Compound	B. P. (°C)	Melting Point of Derivative (°C)
			Sulfone				Sulfone
1	Methyl	38-9	109	4	Methylethyl	65-7	36
2	Ethyl	90-2	70-71 (73-4)	5	Phenyl	296	128
3	*n*-Butyl	186-9	43.5	6	*p*-Tolyl	*m.p.* 57.3	158-9

TABLE 39
Sulfonyl Chlorides

	Name of Compound	B. P. (°C)	M. P. (°C)	Melting Point of Derivatives (°C)		
				Acid	Amide	Anilide
1	Methane-	60°/21 mm	liq.	liq.	90	100.5 (99)
2	Ethane-	70°/20 mm	liq.	cryst	60 (58)	58
3	1-Propane-	67/9 mm	liq.		52	+10 (−10)
4	2-Propane-	61/9 mm	liq.	100	60	84
5	1-Butane-	75/10 mm	liq.	syrup	45	−35 (10-15)
6	2-Methyl-1-propane-		liq.	syrup	14-16	38.5
7	Isopentane- (3-Methyl-1-butane-)		liq.	cryst.	3	42
8	Cyclohexane-		oil	90-92		87
9	*o*-Toluene-		10	57	156 (153)	136
10	*m*-Toluene-		12		108	96
11	Benzene-		14.5	52-3[a]	155 (153)	110
12	1-Heptane-		16		75	
13	3,4-Dichlorobenzene-		22.4		140 (135)	
14	*o*-Chlorobenzene-		28.5		188	
15	2,4-Dimethylbenzene-		34		138	
16	2,5-Dichlorobenzene-		38	93-97	186 (180)	160
17	*o*-Bromobenzene-		51		186	
18	*p*-Chlorobenzene-		51.5* (53)	68 (92-3)	144	104
19	2-Chloro-4-methylbenzene-		52-54		184-5	
20	Cetyl-		54	54	97	
21	1,3-Benzenedi-		63		229	148-50
22	*m*-Nitrobenzene-		64		167	126
23	*d*-Camphor-10-		67	193	132	121
24	1-Naphthalene-		68 (66)	90	150	112 (132)
25	*o*-Nitrobenzene-		69	85 (70)	191 (193)	115
26	*p*-Toluene-		69	103-4 (92)	137	103
27	*p*-Bromobenzene-		76	88-90 (103)	166 (161)	119
28	2-Naphthalene-		76	91 (122)	217 (213)	132
29	*p*-Nitrobenzene-		80	109-11 (95)	180	171 (136)
30	*d*-Camphor-3-		88		143	124
31	Benzyl- (α-Toluene-)		92	cryst.	105	102
32	3,5-Dimethylbenzene-		94		135	119
33	Ethylenedi-		95	104*		69
34	2,4-Dinitrobenzene-		102		154 (157)	
35	1-Nitro-2-naphthalene-		121	105	214	202
36	1,2-Benzenedi-		133		252	241
37	*d*-Camphor-8-		138		137	
38	1,4-Benzenedi-		138-9		288	249
39	1,4-Naphthalenedi-		166		273	
40	Anthraquinone-β-		197		261	193
41	Biphenyl-4,4′-di-		203	72	300	

[a] Benzene sulfonic acid wet melts at 43-4; dry, *m* 50-1; anh., *m* 52-3; after distillation under extreme low pressure (0.001 mm), *m* 65-6.

TABLE 40
Sulfonamides[a]

	Name of Compound	M. P. (°C)
1	Isopentane- (2-Methylbutane-)	3
2	1-Butane-	45
3	1-Propane-	52
4	Ethane-	60 (58)
5	2-Propane-	60
6	1-Heptane-	75
7	Methane-	90
8	Cetyl- (Hexadecane-)	97
9	2-Ethylbenzene-	100
10	Benzyl- (Toluene-α-)	105
11	*m*-Toluene-	108
12	3,5-Dimethylbenzene-	135
13	*d*-Camphor-8-	137
14	*p*-Toluene-	137
15	2,4-Dimethylbenzene-	137-8
16	*o*-Nitrobenzyl- (*o*-Nitrotoluene-α-)	137
17	3,4-Dichlorobenzene-	140 (135)
18	*m*-Aminobenzene-	142
19	*d*-Camphor-3-	143
20	*p*-Chlorobenzene-	144
21	*m*-Chlorobenzene-	148
22	1-Naphthalene-	150
23	*o*-Aminobenzene-	153
24	*m*-Bromobenzene-	154
25	Benzene-	155 (153)
26	2,4-Dinitrobenzene-	154 (157)
27	*o*-Toluene-	156 (153)
28	*m*-Nitrobenzyl- (*m*-Nitrotoluene-α-)	159
29	*p*-Aminobenzene-	163 (165)
30	*m*-Nitrobenzene-	166 (168)
31	*p*-Bromobenzene-	166 (161)
32	*p*-Nitrobenzene-	180
33	2,5-Dichlorobenzene-	186 (180)
34	*o*-Bromobenzene-	186
35	*o*-Chlorobenzene-	188
36	*o*-Nitrobenzene-	193
37	*p*-Nitrobenzyl- (*p*-Nitrotoluene-α-)	200
38	*p*-Iodobenzyl- (*p*-Iodotoluene-α-)	206
39	2-Naphthalene-	217 (213)
40	*o*-Sulfobenzoic imide (saccharin)	220 (199)
41	2,7-Naphthalene di-	242
42	1,5-Anthraquinone di-	246
43	1,2-Benzenedi-	254
44	Anthraquinone-*p*-	261
45	1,4-Naphthalenedi-	273
46	1,4-Benzenedi-	288
47	1,6-Naphthalenedi-	298
48	1,8-Anthraquinonedi-	340

[a] For the m.p. of N-xanthylsulfonamides that may be used as derivatives, see page 325.

TABLE 41[a]

Sulfonic Acids

	Name of Compound	Melting Point of Derivatives (°C)			
		Thiuronium	*p*-Toluidine salt	Aniline salt	*o*-Toluidine salt
1	Acetylnaphionic		232-3	231-2	
2	*o*-Aminobenzene-			180-210*d*	
3	1-Amino-8-naphthol-3,6-di-	312*d*	335*d*	340*d*	320*d*
4	Anthraquinone-1-			284	
5	Anthraquinone-2-	211	308	309	
6	Benzene-	147.5-148.5	205	240	176
7	*m*-Benzene-di-	214.3			
8	Benzothiazole-2-	170.5-171.0			
9	*p*-Bromobenzene-		215-216.5	237-238	182-183.5
10	α-Bromocamphor-α-	133.7			
11	*d*-Camphor-	209.7			
12	*m*-Chlorobenzene-		199-200	206-207	
13	*p*-Chlorobenzene-	174.9-175.4	208-210	222-223	162.5-164
14	*m*-Diethylaminobenzene-	182.4			
15	Diphenyl-*p*,*p*′-di-	171.0			
16	Diphenylamine-4-			206.5	
17	Diphenylamine-4,4′-di-			239	
18	Ethyl-	114.7			
19	Naphthalene-1-		181	183	237
20	Naphthalene-1,6-di-		314-315*d*	298-299*d*	323 324*d*
21	Naphthalene-2-		221	269	213
22	Naphthalene-2,7-di-	205*d*	299	251-252	238
23	α-Naphthalene-	136.8			
24	β-Naphthalene-	190.5-190.8			
25	1-Naphthol-2-	169.4			
26	1-Naphthol-4-	103.4	196	186-187	303-304
27	1-Naphthol-4,8-di-	205.2			
28	2-Naphthol-6-	206.7	248	264	208
29	2-Naphthol-8-		232	240	242
30	2-Naphthol-3,6-di-	233.2	250	254	257
31	1-Naphthylamine-4-	195.1*d*			
32	1-Naphthylamine-5-	179.4			
33	1-Naphthylamine-8-	300*d*			
34	1-Naphthylamine-3,6,8-tri-		292*d*	312*d*	304*d*
35	2-Naphthylamine-6-	330*d*			
36	2-Naphthylamine-4,8-di-	209-211*d*			
37	2-Naphthylamine-6,8-di-	276*d*			
38	*m*-Nitrobenzene-	146.1	222	222	193
39	1-Nitronaphthalene-2-			201.9	
40	5-Nitronaphthalene-1-			265*d*	
41	5-Nitronaphthalene-2-			260*d*	
42	*p*-Phenol-	168.7	202	170	192
43	*N*-Phenyl-1-naphthylamine-8-	182-189*d*			
44	Sulfanilic	184.5-185			
45	*o*-Sulfobenzoic		197	165	127.5
46	*m*-Sulfobenzoic (mono salt)			224-226	
47	Thymolsulfonic	212.4			
48	*o*-Toluene-		203-204	218	
49	*p*-Toluene-	181-182	198	238	190
50	*o*-Xylene-	207.6-208.1			
51	*m*-Xylene-	145.6-146.1			
52	*p*-Xylene-	183.7			

[a] In the absence of data on *m.p.* or *b.p.* of the sulfonic acids the compounds listed have been arranged in alphabetical order.

Miscellaneous and Physiologically Active Compounds (Drugs, Vitamins, Hormones, Heterocyclic Bases)

Quinoxaline: M.P. 30.5(28); B.P. 229. Q·HCl: 184*d*; Q·H_2SO_4: *m* 186–7; Q·oxalate: *m* 169; Q·methiodide: *m* 176*d*. $KMnO_4$ → pyrazine-2,3-dicarboxylic acid: *m* 193*d* [Gabriel and Sonn, *Ber.*, **40**, 4851], whose diamide *m* 240*d* (*ibid.*); Na and EtOH → 1,2,3,4-tetrahydroquinoxaline: *m* 97, *b* 289, which alk. $K_3Fe(CN)_6$ reconverts to quinoxaline.

***l*-Ephedrine: M.P. 40(43); B.P. 225*d*.** $[\alpha]_D^{20}$ −6.3 in EtOH; E·HCl: *m* 218(214–16); E·HBr: *m* 205; E·H_2PtCl_6: *m* 186; E·$HAuCl_4$: *m* 128–31; N-*p*-nitrobenzoyl deriv.: *m* 187–8. Pptd. by $Na_2S_2O_3$-HgI (new alkaloid reagent) [Wachsmuth, C.A. **37**, 5197]. For two new color reactions, see M. Pesez, C.A. **38**, 5168. For microscopic identification, see van Zijp, C.A. **38**, 2448[9]; *l*-ephedrine synthesis: U.S. Pat. 1956950 (May 1, 1934) to Hildebrandt and Klavehn; also another method described by Kamlet in *Drug Trade News*, *v.* **16**, no. 16, p. 27 [C.A. **36**, 3820], which see for further information on ephedrine and bibliography. Identification: 10 mg in 1 ml H_2O and 1 or 2 drops HCl; add 0.1 ml $CuSO_4$ soln.; then 1 ml 1 : 5 NaOH soln. → red-purple color. Add 1 ml Et_2O and shake well. The purple becomes aquamarine blue; the hydrochloride with $K_3Fe(CN)_6$ gives odor of benzaldehyde; CS_2 and $CuSO_4$ → olive-brown color; $CuSO_4$ and NaOH → violet color.

4-Phenyl-3-buten-2-one (Benzalacetone; Methylstyryl ketone; Acetocinnamone): M.P. 42; B.P. 262. Has a persistent, pungent, coumarin-like odor. Oxime: *m* 117(116, 115); phenylhydrazone: 159 (156–7); *p*-nitrophenylhydrazone: 166; semicarbazone: 187–8 (198); H_2SO_4 → orange-red color; on exposure to air benzalacetone gradually turns brown. Acts as an irritant to the skin [*Org. Syntheses*, Coll. Vol. I (2nd Ed.) p. 77].

Thalline: M.P. 42–3; B.P. 283. T_2·HI : 155–6; N-acetyl: 46–7; picrate: 162; oxidizing agents → emerald green; boiling with $FeCl_3$ → brownish-green or rose.

Triphenyl phosphate: M.P. 49; B.P. 245(11 mm); D.25 = 1.301. Heated in abs. EtOH with Na → phenetole: *b* 172; with $Ba(OH)_2$ → phenol: *m* 42, and Ba diphenylphosphate: *m* 61. H_2SO_4 and HNO_3 → tri-*p*-nitroderivative: *m* 155. Heated with KCN → benzonitrile: *b* 190, and phenol: *m* 42.

Tropacocaine: M.P. 49. Benzoyl derivative of pseudotropine; T·HCl: 283; T·$HAuCl_4$: 208; T·C_6H_5·COOH: 60–1; N-oxide: 152–3 (formed by H_2O_2 action); its hydrochloride *m* 200; picrate: 240–2 (darkens at 215–20); hot conc. HCl → pseudotropine (*m* 108–9); resorcinol and H_2SO_4 → yellow → violet → red color; 2-naphthol and H_2SO_4 → grey → dark blue.

***o*-4-Xylidine: M.P. 51(49); B.P. 226.** X·HCl: 256; N-acetyl: 99; N-cinnamoyl: 175–6; N-formyl: 52.

Cyanogen bromide: M.P. 52(49–51); B.P. 61.4. In acid and thiosulfate reacts rapidly and smoothly acc. to the equation BrCN + $2S_2O_3$ + H → Br + HCN + S_4O_6 [Lang, *Z. Anal. Chem.*, **67**, 3]; reacts with furan to form bromofuran ($HgCl_2$ derivative *m* 175), Klopp and Wright, *J. Org. Chem.*, **4**, 42–9, C.A. **33**, 5844. For properties and detection, see Diescrens, C.A. **34**, 2951, and *Org. Syntheses*, Coll. Vol. II, p. 150.

Indole: M.P. 53: B.P. 254. H_2O_2 → indigotin (subl. 392); N-benzoyl: *m* 67–8; N-acetyl: 182–3, sublimable (Baeyer, *Ber.*, **12**, 1314); N-nitroso: 171–2d; picrate, long red needles (Baeyer, *loc. cit.*); I·$C_6H_3(NO_3)_3$ (1 : 3 : 5) : 187. Montignie's reaction [*Bull. Soc. Chim.* (4) **51**, 689]; boiling aq. soln. with 8–10 drops 10% SeO_2 soln. and 1 ml conc. HNO_3 → violet color, sensitive to 0.05 mg indole. Pine splint reaction cherry red; very sensitive: Na-nitroprusside and KOH soln. → violet color, stable to acetic acid; compd. with *β*-Naphthoquinonesodium monosulfate [Herter and Foster, *J. Biol. Chem.*, **1**, 257], bluish well-built needles down to 1 : 256,-000 dilution, and then green to 1 : 1,000,000. $CHCl_3$ takes it up with a rose color; addn. of alc. soln. of *p*-dimethylaminobenzaldehyde and then dropwise of 25% HCl acid → red, then add 0.5% soln. of $NaNO_2$ → dark red [Steensma, *Z. Physiol. Chem.*, **47**, 15; Weehuizen, *Pharm. Week Bl.*, **45**, 1325; Blumenthal et al., *Biochem. Z.*, **19**, 526; Salkowski, *ibid.*, **97**, 123; *Biochem. J.*, **1934**, 1171.] Use of xanthydrol: C.A. **38**, 3570[8]; Winterstein, *Z. physiol. Chem.*, **105**, 25.

N,N-Dimethyl-*p*-phenylenediamine (*p*-Aminodimethylaniline): M.P. 53(41, 36); B.P. 263.3. Structure: $H_2N·C_6H_4·N(CH_3)_2$; not to be confused with (sym.) N,N-dimethyl-*p*-phenylenediamine, $C_6H_4(NH\ CH_3)_2$, which has a similar melting point; provokes unbearable burning of the skin and is poisonous. Easily reacts with

[a] See page 327 for a brief discussion on the compounds listed in this table.
[b] Except with those references for which no volume number is given, the date of publication has been omitted from all literature references throughout this table. For abbreviations used in this table see page 355.
[c] The compounds are listed in the order of increasing melting points.

Miscellaneous and Physiologically Active Compounds (Drugs, Vitamins, Hormones, Heterocyclic Bases)

benzaldehyde to form N,N-dimethyl-N'-benzal-p-phenylenediamine: *m* 101(99, 93) [Moore and Gale, *J. Am. Chem. Soc.*, **30**, 399]. Treated in acid soln. with H_2S and $FeCl_3$ → methylene blue [Caro, Ger. Pat. 1886 of Dec. 15, 1877; A. Bernthsen, *Ann.*, **251**, 19]; on this reaction is based its use for detection of H_2S [E. Fischer, *Ber.*, **16**, 2235]; AcOH soln. added to soln. of 1 at. wt. Br in AcOH gives an addition compd.: *m* 146-7, green cryst. with metallic lustre [Willstatter and Piccard, *Ber.*, **41**, 1469]; MnO_2 and H_2SO_4 oxidizes to quinone; N'-acetyl: *m* 132-3(129) [Meldola and Hollely, *J. Chem. Soc.*, **107**, 618]; N',N'-diacetyl: 68-9; N'-benzoyl: 228(223-4); N',N-dibenzoyl: 240 [Stolle, *Ber.*, **45**, 2684]; N'-chloracetyl: 146-7; N'-*p*-nitrobenzoyl: 258; picrate: 139; a trace can be detected by boiling up in a test tube closed with a filter paper soaked in $HgNO_3$ soln.; on cooling, the bottom of the filter paper will be colored green if dimethyl-p-phenylenediamine was present [Mohlau, *Ber.*, **16**, 2011]; if warmed with H_2O_2 and C_6H_5OH and NaOH soln. and then acidified, the liquid is colored a deep blue (formation of indophenol or phenol blue $C_{14}H_{14}N_2O$).

Vitamin K_2: M.P. 54. Yellow cryst. solid [Binkley et al., *J. Biol. Chem.*, **133**, 721(1940)]. Vitamin K_1: *m* −20, yellow oil [*J. Am. Chem. Soc.*, **61**, 2557].

Quinine hydrate (anhyd.; + $3H_2O$, lost at 125): M.P. 57. See quinine, M.P. 177.

l-Scopolamine (Hyoscine, $C_{17}H_{21}NO_4 + H_2O$): M.P. 59. S·HBr (and $3H_2O$): 190-2; $[\alpha]_D^{16.8}$ 25°45'; picrate: 190-1; alcoholic solution does not precipitate HgO from $HgCl_2$ solution (diffn. from atropine).

Procaine (Novocaine, + $2H_2O$, *m* 51) M.P. 61. P·HCl: 153-6; P·HI: 121-2; P·HNO_3: 100-2; borate: 168(159-60); picrate: 146-7; P·*p*-NH_2·C_6H_4COOH: 104 [Einhorn and Uhlfelder, *Ann.*, **371**, 136].

Vitamin A: M.P. 63-4. Distills at 120-5 and 5 x 10^{-3} mm; optically inactive, but destroyed by ultraviolet light; yellow prisms, fat-soluble, [Baxter and Robeson, *J. Am. Chem. Soc.*, **64**, 2411]. Readily autoxidizes. Stable to heat in inert atm.; identified by the characteristic color reaction given by $SbCl_3$ in $CHCl_3$ [Carr and Price, *Biochem. J.*, **20**, 497]; oxidation with ozone → geronic acid (liq. *b* 275-80 at 740 mm), oxime: 93-4; semicarbazone: 164; 2,4-dinitrophenylhydrazone: 135.5-7; acetate; 56-8; disuccinate: 73-5; β-naphthoate: 76; anthraquinone-β-carboxylic ester: 126.

Trioxymethylene: M.P. 64; B.P. 114.5. (Not to be confused with paraformaldehyde); sublimes at 46 undecomposed in presence of moisture; condenses with 2,4-dichlorophenol to 3,5-dichlorosaligenin methyl ether [Ziegler and Simmler, *Ber.*, **74**, 1871-9; C.A. **36**, 5154].

Benzohydrol: M.P. 69; B.P. 297(748 mm). Acetyl: 41-2; 3,5-dinitrobenzoyl: 142; *p*-diphenylurethane: 197; conc. H_2SO_4 gives deep red coloration; oxidizes to benzophenone by CrO_3 and H_2SO_4.

Emetine: M.P. 74(68). Sensitive to light; E·2HCl: 235-55 $[\alpha]_D + 21$; E·2HBr: 250-65 $[\alpha]_D + 15.2$; E·$2HNO_3$: 245; E·H_2SO_4: 205-45.

N-Phenyl-*p*-phenylenediamine (*p*-Aminodiphenylamine): M.P. 75(66); B.P. 354. N-Acetyl: 158; N-benzoyl, red needles (from EtOH). The hydrochloride gives with $FeCl_3$ or other oxidizing agents a green-black ppt. of emeraldin; heated with S → aminothiodiphenylamine; P·$2C_6H_3(NO_2)_3$1,3,5, *m* 105 [Sudborough, *J. Chem. Soc.*, **109**, 1346].

Trional (Methylsulfonal): M.P. 76. Differentiated from sulfonal in that resorcinol and H_2SO_4 give green color; when, after dilution, NH_3 is then added, sulfonal gives a bright rose color, trional a yellow to red-brown color [Ekkert, *Pharm. Zentralh.*, **71**, 550; C.A. **25**, 170, 1633].

Alantolactone (Helenin): M.P. 76; B.P. 275. HCl: 117; HBr: 106; di-HCl: 134*d*; di-HBr: 117.

Chloretone + ½H_2O (1,1,1-Trichloro-2-methyl-2-propanol; Chlorobutanol; Acetone-chloroform): M.P. 80-81; B.P. 167. The anh. compd. *m* 97. Hypnotic and germicide. *m*-Nitrobenzoyl: *m* 86-8 (C.A. **17**, 1969[1]). For ident., see Aldroch, *J. Biol. Chem.*, **34**, 263; *J. Am. Chem. Soc.*, **42**, 1502.

Vitamin D_3 ($C_{27}H_{44}O$; 7-Dehydrocholesterol): M.P. 82-4. 3,5-Dinitrobenzoate: *m* 129 and 140; allophanate: *m* 173-4, (dimorphous); *p*-nitrobenzoate: 127.

Dichloramine-T: M.P. 83(78-84). Structure: *p*-toluenesulfodichloramide. Prisms or white powder almost insoluble in water, with odor resembling that of chloride of lime. Benzoyl derivative: *m* 147-50. Anhydrous soln. of compd. in dry Me_2CO, C_6H_6, or CCl_4 warmed with Hg (e.g. 25 ml Me_2CO containing 20 g Hg) gives a bulky white ppt. of HgCl and the mercuric salt of toluene-*p*-sulfonamide [Waters, *J. Chem. Soc.*, **1937**, 2010; Roberts, *ibid.*, **1923**, 2711].

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Lignoceric acid: M.P. 83.5(80–1). Methyl ester: 59(57); phenacyl ester: 87–8; *p*-chlorophenacyl ester: 99–100; *p*-bromophenacyl ester: 90–1; cholesteryl ester: *m* 87.

Indoxyl (3-Hydroxyindole): M.P. 85; B.P. *d*. Yellow crystals, sol. in warm water with yellowish green fluorescence; oxidizes to indigotin, and condenses with isatin to indirubin [Baeyer, *Ber.*, **14,** 1744]; N-acetyl: 139 (its oxime-HCl *m* 139, its phenylhydrazone *m* 154). See Madelung and Haller, *Ber.*, **57,** 241–52; C.A. **18,** 2164; also Spencer, *J. Soc. Chem. Ind.*, 50T, 64; C.A. **25,** 2144. N-Benzoyl: 123(133); 1,3-diacetyl: 82; distinguished from indole by the urocarmine reaction, Fearon and Thompson, *Biochem. J.*, **24,** 1371–8; e.g., resorcinol and indoxyl condense to form a carmine-red dye when oxidized, C.A. **25,** 720. Likewise *o*-cresol yields *o*-cresol indogenide: *m* 196–9 (uncorr.) (*ibid.*); to detect small amounts, use benzenediazonium chloride, yielding in acid soln. 2-benzeneazoindoxyl: *m* 236*d* [Baeyer, *Ber.*, **16,** 2190]. $FeCl_3$ colors it dark red in alc. soln.

Physostigmine: M.P. 86–7; also melts at 105–6; see page 448.

Imidazole (Glyoxaline): M.P. 90; B.P. 255. Benzoyl: *m* 202–3; $I\cdot HAuCl_4$: 230*d*; $I\cdot AuCl_3$: 190*d*.

Benzocaine (Ethyl *p*-aminobenzoate): M.P. 92. B·HCl: *m* 207–8; picrate: 131; N-benzoyl: 148; N-acetyl: 110; N-chloracetyl: 116. See Table 19, page 406, Compound 35.

Acenaphthylene: M.P. 92–3; B.P. 265–75*d*. Picrate: *m* 201–2; 1,3,5-$C_6H_3(NO_2)_3$: 221. Bromination gives 1,2-dibromoacenaphthene: *m* 121–3; OsO_4 compound: *m* 263 [Criegee, *Ann.*, **522,** 87; C.A. **30,** 3811].

Skatole (3-Methylindole): M.P. 95; B.P. 266. $S_2\cdot HCl$: 167–8; N-acetyl: 68; picrate: 45; condenses with phthalimide to greenish-yellow plates: *m* 186.7 [Bogert and Ruderman, *J. Am. Chem. Soc.*, **44,** 2613]; $K_4Fe(CN)_6$ and H_2SO_4 → violet; see indole (*m* 53) reactions, in which it is differentiated from indole as follows: (a) Steensma reaction → blue-violet, and on adding nitrite → dark blue; (b) Na nitroprusside and KOH → yellowish; only after boiling with AcOH → violet. For another differentiation from indole, see Sasaki, *Biochem. Z.*, **23,** 402. Alc. soln. of compd. mixed with HCl acid does not color a pine splint, but if a splint of the wood is moistened with soln. of skatole and introduced into strong HCl acid, then it is colored a cherry red and later violet.

Acenaphthene: M.P. 95; B.P. 277.5. Addition compd. with 1,3,5-$C_6H_3(NO_2)_3$: *m* 168; picrate: 162 (orange-red). Note: Impure product melts at higher t° (fluorene), and therefore the B.P. is a better criterion of purity [Graebe and Bossel, *Ann.*, **209,** 207 *Anm.*, 1896]. Benzal chloride and H_2SO_4 → intensely dark blue; in chloroform soln. and arom. aldehydes → green turning to reddish violet [deFazi, in *Ber. von Schimmel and Co.*, Apr.–Oct., **1917,** p. 119].

Flavone: M.P. 97. Oxime: *m* 237.

***l*-α-Cocaine: M.P. 98.** C·HCl: *m* 197(186; 183); $[\alpha]_D - 71.95$; $C_2\cdot H_2CrO_4\cdot H_2O$: 127 (yellow ppt. from K_2CrO_4 and HCl); methiodide: 169 (164); styphnate: 187; picrate: 165–6. For detection see Bamford, *The Analyst,* **63,** 645–9. Identified by the following reaction: 100 mg in 0.4 ml *N* HCl and H_2O to 5 ml; add 5 drops of 1 : 20 soln. of CrO_3 → yellow ppt. redissolving on shaking; on addition of 1 ml HCl, a permanent orange ppt. results. Addition to diazotized soln. of compd. with 1,8-dihydroxynaphthalene-3,6-disulfonic acid, followed by NH_4OH, gives intense red-violet color [C.A. **38,** 6491].

***o*-Phthalaldehydic acid: M.P. 99(95–6).** Ethyl ester: *m* 64, *b* 240–3; benzoylhydrazone: *m* 189*d*; azine: 211, which with boiling water → phthalazone: *m* 183–4 (subl. 100); [Liebermann and Bistrzycki, Ber., **26,** 532]; semicarbazone: 202; phenylhydrazone: 107–8 (106); anhydride ($C_{10}H_{10}O_5$): 221; oxime: 120 (rapidly heated) → phthalimide: *m* 238; anil.: 174.

Homatropine: M.P. 99–100(93.5–98.5). Not the same as homotropine ($C_9H_{17}ON$: *m* 85). H·HCl: prisms *m* 219–27; H·HBr: 217–8; $H_2\cdot H_2SO_4$: 222–6; methobromide: 192–6; methyl ether cryst. with 2 mol. of H_2O: *m* 50–5; forms picrate: *m* 238 and picrolonate: *m* 226. Compd. with picric acid → yellow ppt.; with $AuCl_3$ → amorphous, later cryst. ppt. [Glycart, *J. Assoc. Official Agr. Chem.*, **18,** 521]. Na and HCO_2Et → formyl phenacetyltropine: *m* 214*d*, forming oxime which *m* 139*d* [Asahina and Nogami, see C.A. **34,** 6940].

Xanthene ($C_{13}H_{10}O$: Dibenzopyran): M.P. 100.5 (98.5); B.P. 315(310–2). Volatile with steam. Slowly sublimes below M.P.; oxdn. → xanthone: *m* 174.

17-Equilenone I: M.P. 100–1. Picrate: *m* 110 [Bachmann and Wilds, *J. Am. Chem. Soc.*, 62, 2084 (1940)].

***p,p'*-Tetramethyldiaminobenzohydrol (Michler's hydrol): M.P. 102–3 (96–8).** For discussion of M.P. of compd., see *Z. F. Farben-Text. Chemie.* **1** : 1. Dimethiodide: *m* 195; benzyl ether (from ligroin): 102–3; 1,3,5-$C_6H_3(NO_2)_3$: 75.5; addition compd. with benzoquinone: green crystals

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m 169–70 [Bennett and Willis, *J. Chem. Soc.*, **1929**, 267]. Dissolves in glacial AcOH giving blue color.

Piperazine: M.P. 104; B.P. 146(140). Compd. with $6H_2O$: *m* 44; *b* 125–30. $P_2 \cdot 2C_6H_5OH$: 99–101. For use of compd. to identify fatty acids, see Pollard et al., *J. Am Chem. Soc.*, **56,** 1759–60. Picrate: 280*d*, N-(mono)acetyl: 52; N,N-di-acetyl: 144(138, 134); N-(mono)benzoyl: 75; N,N-dibenzoyl: 196(191); N-*p*-toluenesulfonyl: 173 (sinters 168); N,N-dinitroso: 158; N,N-dibenzenesulfonyl: 282–3. $FeCl_3$ → bluish-violet. Acetaldehyde and Na-nitroprusside → intense blue (becoming rose-red with AcOH), finally forming a yellow ppt. *p*-Nitrophenol compd.: *m* 144 [Hromatka and Engel, *Ber.*, **76,** 712–17; C.A. **38,** 2628].

Brucinehydrate: M.P. 105. See Brucine: M.P. 178.

Physostigmine: M.P. 105–6; (also M.P. 86–7; Eserine). $P_2 \cdot H_2SO_4$: *m* 145; P·2HBr: 224–6; $P \cdot 2HAuCl_4$: 163–5; N-benzoyl: 115 6; picrate: 114(112–4); also 103–6 [Oliverio and Trucco, C.A. 35, 7116]; salicylate: 185–7(179). HNO_3 → yellow color changing to red on warming, and leaving a green residue upon evaporation.

2-Methyl-1,4-naphthoquinone: M.P. 106. Lemon-yellow cryst. powder with a faint but characteristic odor. Occurs in Vitamin K [Heilbron et al., *J. Chem. Soc.*, **1936,** 905].

Vitamin D_4: M.P. 107–8. $[\alpha]_D^{20}$ + 89.3 (in acetone). 3,5-Dinitrobenzoate: *m* 135–6; $[\alpha]_D^{20}$ + 95.4 (in acetone): [Windaus and Trautmann, *Z. Physiol. Chem.*, **247,** 185].

Digitoxose: M.P. 108–9. $[\alpha]_D^{17}$ + 46.3 in H_2O. Oxime: *m* 102; phenylhydrazone: 204–9.

***l*-Hyoscyamine: M.P. 108.5.** H·HBr: *m* 152 (deliq.); $H_2 \cdot H_2SO_4 2H_2O$ (anh.): *m* 206; $H \cdot (COOH)_2$: 176, picrate: 165; methobromide: 165; $H \cdot HAuCl_4$: 165.

Pyramidone (Aminopyrine): M.P. 109(108). P·HBr: *m* 190; citrate: 85; methiodide: 220*d*; picrate: 168–70; styphnate: 191. $FeCl_3$ → bluish violet color.

***o,o'*-Biphenol: M.P. 109; B.P. 325–6(315).** Zn dust distn. → biphenyl: *m* 71; compd. hydrate: 73–5. $FeCl_3$ → reddish violet color. Diacetyl: 95; dimethyl ether: 155.

Acridine (subl. 100): M.P. 111; B.P. 360. Pungent odor, sternutatory. NaHg → acridan: *m* 169 (subl.), which is reconverted to acridine by CrO_3. With $C_6H_3(NO_2)_3$ forms addn. compd.: *m* 115; $(A \cdot HCl)_2 \cdot HgCl_2$: 235; $A \cdot CH_3COCl$: 236; 4,6-dinitro-*o*-cresol compd.: 168 [Wain, *Ann. Applied Biol.*, **29,** 301–8; C.A. **37,** 2124]. Solutions of compd. fluoresce (use in identification: C.A. **37,** 6207). For other recent tests, see C.A. **36,** 5732 and 6446.

***d*-Galactonic γ-lactone: M.P. 112(90–2); B.P. *d*.** Needles with one mol. H_2O: *m* 66. Semicarbazone: 189.

Antipyrine: M.P. 114; B.P. 319. Compd. with $POCl_3$ → chloride $C_{11}H_{12}N_2Cl_2$: *m* 137; picrate: 188; salicylate: 92; acetylsalicylate: 65; tannic acid T.S. → abundant white ppt.

Vitamin D_2 (Calciferol; $C_{28}H_{44}O$): M.P. 116. Thermolabile (160–90*d*). *p*-Nitrobenzoate: *m* 93; 3,5-dinitrobenzoate: 148–9; phenylurethane: 122; allophanate: 194–5. Compd. with $SbCl_3$ in $CHCl_3$ → deep yellow color [Windaus and Bock, *Z. Physiol. Chem.*, **245,** 168(1936)].

Hydrastinine: M.P. 117. Fluoresces yellow in soln. H·HCl: *m* 212*d*; N-benzoate: 98–9; N-acetyl: 105; oxime: 145–6; methiodide: 267.

Hordenine: M.P. 117. Subl. 140–50; $H_2 \cdot H_2SO_4$ ($2H_2O$): *m* 209–11(205); H·HCl: 176–7; benzoate: 47–8; picrate: 139–40; methiodide: 229–30.

Lumisterol: M.P. 118. 3,5-Dinitrobenzoate: *m* 139–41; acetyl: 100; allophanate: 217–8.

Atropine: M.P. 118(114–15). A·HCl: *m* 165; A·HBr: 163–4; $A_2 \cdot H_2SO_4$ (anh.): 194; $A_2(COOH)_2$: 198; picrate: 175–6; styphnate: 180. See C.A. **33,** 9201, *J. Chem. Soc.*, **95,** 1966.

Sulfosalicylic acid: M.P. 120; B.P. *d*. Crystallizes with $2H_2O$; very sol. in H_2O, EtOH. Above M.P. decomp. to phenol and salicylic acid. Used as reagent for albumin, and as a colorimetric reagent for ferric ion, with which it gives a violet color.

cis-Testosterone propionate: M.P. 121–3. Semicarbazone: *m* 221*d*; oxime: 223. cis-Testosterone: *m* 220–1; acetate: 116; benzoate: 137. For trans-compd. and ident., see *Helv. Chim. Acta*, **18,** 1487; C.A. **35,** 3040.

Xanthydrol: M.P. 123. Reagent for amides (see page 269). H_2SO_4 → yellow color with green fluorescence. Warmed in air → xanthone. Forms salts with mineral acids. For action of heat on xanthydrol, see Schonberg and Mustafa, *J. Chem. Soc.*, **1944,** 305.

Fluorescin (Resorcinolphthalin): M.P. 125–7. Needles from AcOH. Turns yellow in air. Oxdn. → fluorescein: *m* 314–6*d*; dimethyl ether: 204–5; diacetyl: 200–2.

Sulfonal: M.P. 126; B.P. 300. White odorless crystals subl. at 66; sol. in H_2O, EtOH, Et_2O, and $CHCl_3$. Extraordinarily stable to reagents: not affected by H_2SO_4, HNO_3, $KMnO_4$, and Br_2. No special reagents are known; for its detection, see ref. in C.A. **34,** 3447.

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3-Methyl-1-phenyl-5-pyrazolone: M.P. 127. Forms metallic salts with Cu, Co. $FeCl_3$ → pyrazole blue; $M \cdot HCl \cdot H_2O$: 96; $M_2 \cdot H_2PtCl_6 \cdot 4H_2O$ (yellowish-red prisms): 110; ethylenediamine salt: 204; 4-isonitroso deriv. (orange needles): 157(152); 1,3,5-$C_6H_3(NO_2)_3$ addn.: 92; the N-methyl deriv. is antipyrine: *m* 114, *q.v.*

***p*-Aminoazobenzene: M.P. 127.4; B.P. 360.** A·HBr: *m* 206; A·$HgCl_2$: *m* 170; N-acetyl: 144 6 (143, 141); see Pawlewski, *Ber.*, **35**, 113; Berju, *Ber.*, **17**, 1400; N-benzoyl: 211 (205); 1,3,5-trinitrobenzene deriv.: 156–7. Reduction with conc. HCl → aniline and *p*-phenylenediamine. Oxidation → benzoquinone.

***α*-Progesterone: M.P. 128.5; *β*- ; M.P. 121–2.** Dioxime: *m* 243; see Butenandt, *Z. physiol. Chem.* **227**, 93.

Geneserin (Eseridine): M.P. 128–9. Also known as physostigmine oxide. Salicylate: *m* 89–90; picrate: 175; methiodide: 215.

Nicotinamide (Niacinamide, Vitamin P-P): M.P. 129(129–31). White sl. deliq. powder with faint arom. odor. Sol. in H_2O 1 g/ml, EtOH 0 66/ml, sl. sol. Et_2O and C_6H_6. Distills at 150–60 and 5 x 10^{-4} mm. May be recrystallized from $CHCl_3$ and C_6H_6; can be extracted by ether from aq. soln. containing nicotinic acid, which remains in the water. Fused with 2,4-dinitrochlorobenzene, and then dissolved in EtOH KOH → color reaction [Vongerichte, *Ber.*, **32**, 2571]; free nicotinic acid also gives this test, as do many other pyridine derivatives. Chloraurate: *m* 205. Hydrolyzed to nicotinic acid: *m* 237.

5-Nitro-2-toluidine: M.P. 129–30. D^{15}: 1.366; N·HCl: *m* 199–200; N·HBr: 240; acetyl: 201.6; *p*-toluenesulfonate: 175; benzenesulfonate: 157–9.

Piperine: M.P. 129.5. Conc. H_2SO_4 → red color. P·HBr: *m* 170; $P_2 \cdot H_2SnBr_6$: 182–4*d*.

1,3-Indandione (1,3-Diketohydrindene): M.P. 130–1. Deep yellow (enol form) in caustic alkali soln. Dioxime: *m* 220–5*d*; phenylhydrazone: 162–3; diphenylhydrazone: 171.

***l*-Hydrastine: M.P. 132.** Salts are unstable; H·HCl: *m* 116; picrate: 184.

Urea: M.P. 132.7. Xanthydrol deriv.: *m* 258–9 [Kny-Jones and Ward, *Analyst*, **54**, 574]; picrate: *m* 142; flavianate: 298–9*d*; U·HNO_3: 163; oxalate: 171. In general urea can be ident. with certainty only in conc. soln. after isolation, for which purpose it is pptd. from as conc. soln. as possible by means of nitric or oxalic acid, or from dilute soln. by means of xanthydrol. The U·HNO_3 salt is dec. by $BaCO_3$, the soln. conc., and the dry residue extracted with EtOH. For biuret reaction, see Wener, *J. Chem. Soc.*, **103**, 2275; for *o*-nitrobenzaldehyde reaction, see Lüdy, *Monatsheft*, **10**, 311; for Fenton's reaction, see *J. Chem. Soc.*, **79**, 807; for furfural-acetone reaction, see Schiff, *Ber*, **10**, 774, and Gassini, *Arch. farm sp.*, **26**, 238.

Bornyl chloride (artificial camphor): M.P. 132 (128). The ordinary product *m* 125; called also "pinene hydrochloride." *p*-Toluidine → bornyl-*p*-toluidine stellate: *m* 33; HCl-ide: *m* 214*d*; *o*-toluidine → bornylderiv.: *m* 55, hydrochloride: *m* 180 [C.A. **5**, 510[4]].

***l*-Naphthaleneacetic acid: M.P. 133.** The M.P. is also given as 106 [Keach, *J. Am. Chem. Soc.*, **55**, 2974]. Amide: *m* 180–1 (159–60, 154); difficult to hydrolyze.

Carminic acid: M.P. 136*d*. Dark red prisms or bright red powder, freely sol. H_2O, EtOH; insol. $CHCl_3$, C_6H_6; reagent for Al. Anilide (red prisms): *m* 189–90*d*; tetraacetyl: 155–70; hexaacetyl: 170*d*; octaacetyl: 155–65.

***o*-Dianisidine: M.P. 137–8.** Turns violet in the air; 4,4′-N-diacetyl: *m* 242–4(231); 4,4′-N-dibenzoate: 236; dipicrate: 225*d*.

Berberine: M.P. 145. Yellow cryst. with 6 mol H_2O. Picrate: *m* 239–40; chlorine water → brown red color, but on addn. of HCl → cherry red color even in dilute soln. For ident. methods: *Hirschlausen Pharmazeutische Zentrahalle*, **47**, 473(1906); *Schmidt and Abderhalden*, *Abt. I. Tl.*, **9**, p. 395; C.A. **35**, 7115[8].

Indazole: M.P. 146.5; B.P. 270. 1-Acetyl: *m* 42; 1-benzoyl: 92–3; 2-*o*-nitrobenzoyl: 186–7 (stable), 141–2 (labile); 2-*m*-nitrobenzoyl: 134 (stable), 142–4 (labile); 2-*p*-nitrobenzoyl: 164–5 (stable), 137–8 (labile).

Papaverine: M.P. 147. P·HCl: *m* 220–1*d* (210–13); benzoate: 145; picrate: 183(179, 154); picrolonate: 221; methiodide: with $4H_2O$: 60–5, anh.: 195; succinate: 171.

***s*-Diphenylguanidine: M.P. 148.5(147); B.P. 170*d*.** Vulcanization accelerator; used also for standardizing acids. D·HNO_3: *m* 195–6*d*; perchlorate: 162; heated at 100 with Ac_2O → acetanilide: 114, and *s*-acetylphenylurea: 183; thiocyanate: 115 [*Chem. Zentr.*, **1939 II**, 3977]; (1 : 1) salt with phenobarbital: 195–6 [Higgins and Dunker, *J. Am. Pharm. Assoc.*, **33**, 310–4; C.A. **38**, 6498].

Cholesterol: M.P. 148.5; B.P. 360*d*. Formyl: *m* 96; acetyl: 114–5; propionyl: 114; benzoate: 150–1; *p*-nitrobenzoate: 190–3. See also Table 6.

Phthalamic acid: M.P. 148–9. Heated at 155 →

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phthalimide (*m* 238). 2,4-Dinitrophenylhydrazone: *m* 298–9.

Tetramethylthiuram disulfide ("Thiuram," "Vulcacit") $(CH_3)_2N\cdot CS\cdot S\cdot S\cdot CS\cdot N(CH_3)_2$: M.P. 150–4(146). Colorless crystals from $CHCl_3$-EtOH; very sol. in $CHCl_3$, sparingly in EtOH and Et_2O. Vulcanization accelerator. Aq. alc. KCN → tetramethylthiuram (mono) sulfide: *m* 104, which alkalis convert into dimethylamine [Braun and Stechele, *Ber.*, **36**, 2280]. Condenses with quinoidine at 130 [see C.A. **30**, 1060, and U.S. Pat. 1923055]. For detn. and detection, see C.A. **30**, 4790; **18**, 1765; **27**, 3112.

Hypoxanthine (Sarcine): M.P. 150*d*. Structure: 6-hydroxypurine. Picrate: *m* 250–4*d*; flavianate: 282. Heated 0.5 hours with Zn and HCl on water bath → transient purple; on filtering and adding NaOH → red color [Kossel, *Z. Physiol. Chem.*, **12**, 252; Fischer, *Ber.*, **30**, 2230].

Flavianic acid (Disodium salt is known as Naphthol Yellow S): M.P. 151. Structure: 2,4-dinitro-1-naphthol-7-sulfonic acid; yellow needles from HCl acid; disodium salt: Naphthol Yellow. Forms ppts. with org. bases: trimethylamine salt: *m* 217–23*d*; betaine salt: 229*d*. Isoamylamine salt: 215–7 [C.A., **23**, 4702[2], and **26**, 4792[8]]. For use in ident. of org. bases, see Langley and Albrecht, *J. Biol. Chem.* **108**, 729–39. For deriv. with amino acids, see *J. Biol. Chem.*, **154**, 549; **78**, 475; C.A. **18**, 1681.

Chlorophyll-a: M.P. 150–3. Formula: $C_{55}H_{72}O_5N_4Mg\cdot\frac{1}{2}H_2O$; the *b*-form melts at 183 5; mixture of *a* and *b* melts below 100.

Bromural (1-Bromoisovalerylurea): M.P. 154. Hypnotic; commercial product usually melts at 147. Compd. has 3 diff. M.P.: 152, 148, 143, representing 3 modifications [Doser, C.A. **38**, 2794[3]]; α-naphthol and conc. H_2SO_4 → rose color, which when heated → yellow to brown (C.A. **26**, 5773[8]).

Codeine: M.P. 155. $C\cdot HCl\cdot 2H_2O$: $[\alpha]_D^{20} - 108.2$. Picrate: *m* 196–7; styphnate: 115; acetyl: 133.5. A very sensitive precipitant in H_3PO_4 soln. is I_2-KI and phosphotungstic acid. CH_2O and H_2SO_4 → blue-violet color. Reactions: like those of morphine. For diffn. from morphine, see *Archiv. der Pharmazie*, **225**, 348.

D-Galacturonic acid: M.P. 159–60. Oxidizes to mucic acid. Phenylhydrazone: *m* 140–1 [Niemann et al., *J. Biol. Chem.*, **101**, 348]; *p*-bromophenylhydrazone: 150–1; brucine salt: 180*d*; cinchonine salt: 178*d*.

Pyridoxine (Vitamin B_6, Adermine): M.P. 160*d* (subl.). Marketed as the hydrochloride, a white, odorless powder with a salty taste, stable to heat but destroyed by light; $C_8H_{11}O_3N$ readily sublimes in vac.; sol. H_2O, EtOH, and Me_2CO. Optically inactive; P·HCl: *m* 206–8*d* white platelets: $FeCl_3$ → red; tribenzoyl: 121–8 [Stiller et al., *J. Am. Chem. Soc.*, **61**, 1237]; picrate: 156. $FeCl_3$ → reddish brown color [Keresztesy and Stevens, *J. Am. Chem. Soc.*, **60**, 1267]; the cyanine-dye test is specific, but complicated by the necessity of first forming the methyl ether with diazomethane [Kuhn and Low, *Ber.*, **72**, 1453]. For identification with sulfanilic acid and p-nitraniline in EtOH soln. (diazotization), see Casida and Hillbain, *Endocrinology*, **18**, 249.

Indophenol: M.P. 160. I·HCl: *m* 310; acetyl: 115–6.

***l*-Quinic acid: M.P. 161.6.** Heated at 200–250 gives the γ-lactone (quinide): *m* 187; NH_4 salt: 179; amide: 132; tetraacetyl: 132–6; tetrabenzoate: 137–8.

Furil: M.P. 161–2(165). Dioxime: *m* [164–8 (162–4).

Cupferron: M.P. 163–4. Structure: Ammonium salt of N-nitroso-β-phenylhydroxylamine. Yellow crystals. Very sensitive specific reagent for U and Ba [Martini, C.A. **23**, 1841]; also precipitant for Fe and Cu; the nitroso base itself: *m* 58–9.

2,3-Cresotic acid (o-Cresotinic): M.P. 163–5; B.P. subl. *p*-Nitrobenzyl ester: *m* 98.5; phenacyl ester: 138.5.

Ergonovine (Ergometrine): M.P. 162–4. E·HCl: *m* 269.

Tyramine (Tyrosamine): M.P. 164–6; B.P. 180. White needles or leaflets; sol. in boiling H_2O; sol. in C_6H_6: T·HCl: *m* 269, sol. in H_2O.

Sulfanilamide (*p* - Aminobenzenesulfonamide): M.P. 165–6(163). N_1,N_4-Dibenzoyl: *m* 268–70; N_4-Benzoyl (from pyridine): *m* 284; N_1-acetyl (from H_2O): 182–4; N_4-acetyl (from aq. alc.): 219; N_1,N_4-diacetyl (from EtOH): 253. Refs.: Northey, *Chem. Rev.*, **27**, 85; Dewing et. al., *J. Chem. Soc.*, **1942**, 239; C.A. **2**, 2551.

Traumatic acid: M.P. 166. Plant hormone: *J. Am. Chem. Soc.*, **61**, 3434 (1939); also *Science*, **90**, 329; U.S. Pat. 2339259. Structure: *p*-toluenesulfonchloramide. Oxidizes with $KMnO_4$ in hot water to Sebacic acid: *m* 133. *S*-benzylthiuronium salt: Donleavy, *J. Am. Chem. Soc.*, **58**, 1004.

Chloramine-T: M.P. 166–85. Addition of a soln. of 2 g KI and 1 g compd. to a soln. of 0.2 g *o*-nitrophenol in 14 ml 0.1 *N* KOH and heating for 2 hours, and then made acid with AcOH → 2,4-diiodo-6-nitrophenol: *m* 98 [Roberts, *J. Chem. Soc.*, **1923**, 123, 2711]. Pyrocatechol soln. with compd. gives deep amethyst violet

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color gradually changing to dirty green. For other color reactions, see C.A. **23**, 1840.

Ergosterol: M.P. 168(162–4). Phenylurethan: *m* 185; $SbCl_3$ in $CHCl_3$ → violet; forms an insol. digitonide. See also Table 6. *Ber.* **65**, 1006.

β-Indoleacetic acid (3-Indoleacetic acid, Heteroauxin): M.P. 168–70 (165). Plant-growth hormone $[\alpha]_D^{20}$ in EtOH: −3.8. Picrate: *m* 177 (174); for fluorescence test, see C.A. **37**, 2306; for color reactions, see C.A. **29**, 2988; **2**, 2578; **38**, 5239. For detection of amounts as small as 8×10^{-14} g by means of cephalaria, see C.A. **32**, 2981.

Picramic acid: M.P. 169. Dark red needles (from EtOH); gives color reactions with proteins, amino acids, and amines, but not with their salts; *p*-nitrobenzoyl: 299–300; *p*-toluenesulfonyl: 191; benzoyl: 230(220); N-benzyl: 139.

Benzimidazole (Benziminazole, benzoglyoxaline, 1,3-benzodiazole): M.P. 170(174). N-Acetyl: *m* 113–4; N-benzoate: 93 (picrate of benzoate: 215); picrate of compd.: 225–6 (223, 220) [See Wagner et. al., *J. Chem. Educ.*, **13**, 266]. Compd. forms copper salt $Cu(C_7H_6N_2)_2$, brick-red ppt. [Skraup, *Ann.*, **419**, 70]. For identification, see C.A. **37**, 113.

Santonin: M.P. 170(172). Sublimes above its M.P. $[\alpha]_D^{15}$ − 175.4. Oxime: *m* 218; semicarbazone: 232*d*; phenylhydrazone: 230–1*d*. Compd. with EtOH-KOH → red color; heated with 50% H_2SO_4 on the water bath till yellow, then on adding a trace of $FeCl_3$ and further warming → violet color [Lindo, *Pharm. J.*, **8**, 464].

Quinhydrone: M.P. 171. Dark-green rhombic prisms. Reduced by $K_2Cr_2O_7$ and dil. H_2SO_4 to quinone: *m* 115–16. Heated with Ac_2O at 160–70 forms hydroquinone diacetate (*m* 121) and quinone.

Piperil: M.P. 171.5. Mono-oxime: *m* 199; dioxime: 244; semicarbazone: 250; phenylhydrazone: occurs in two forms: (I) *m* 183–4*d*, (II) *m* 219–20; alkali → piperonylic acid: 229.

Phthiocol ($C_{11}H_8O_3$): M.P. 171–2(192). Structure: 2-hydroxy-3-methyl-1,4-naphthoquinone or 2-methyl-3-hydroxy-1,4-naphthoquinone [Asano and Hase, C.A. **36**, 2259(1942); Almquist and Klose, *J. Am. Chem. Soc.*, **61**, 1611; Fieser et al., *ibid.*, p. 2206]. Occurs in Vitamin K; NaOEt (or NaOMe) → purple-blue → red → brown. Specific color test: [Fieser, *loc. cit.*].

l-Abietic acid: M.P. 171–4(182, 166). Colorless plates of irregular shape, sharply extinguishing with crossed nicols and exhibiting brilliant polarization. $[\alpha]_D$ − 100 in EtOH; also reported as −104, and −110.5. Sodium tetraabietate: *m* 205–8(170–5); di-*n*-amylamine salt: 141–2; di-*n*-butylamine salt: 158–61; quinine salt: (cryst. from EtOH) 185–7 [Palkin and Harris, *J. Am. Chem. Soc.*, **56**, 1935]. For the Liebermann color reaction, see LaLande, *J. Am. Chem. Soc.*, **55**, 1536–40. For color reaction with furfural, see C.A. **26**, 2612.

Heroine (Diacetylmorphine): M.P. 173(171–2). H·HCl: *m* 231–2; methiodide: 252*d*. A soln of 50 mg of the compd. in 1 ml EtOH and 1 ml H_2SO_4 develops odor of ethyl acetate; if the cooled mixture is added to a soln. of 10 mg $K_3Fe(CN)_6$ which has been mixed with one drop of $FeCl_3$ soln., the brown-red coloration is changed to blue, then a blue ppt. is formed.

Benzimidazole: M.P. 174. See Benzimidazole: M. P. 170.

Phenobarbital (Luminal): M.P. 174. Structure: 5-ethyl-5-phenylbarbituric acid. Forms compound with quinine: *m* 183; with hydroquinine *m* 165. For specific reagents, see C.A. **38**, 2454; **37**, 3557; **35**, 8208; **29**, 887. Boiled with NaOH soln. evolves NH_3. Mix 200 mg with 500 mg KNO_3 and 2 ml H_2SO_4 in a tube and immerse in boiling water for 20 minutes. Cool, add 3 ml of water and, cautiously, aqueous ammonia until alkaline. Boil till N_2 evolution ceases; cool, add 2 drops of ammonium sulfide soln. without mixing → brown → red ring is formed and finally orange-red ppt. See also C.A. **38**, 2454.

Quinidine: M.P. 174–5 subl. Optical isomer of quinine, being dextrotatory whereas quinine is levorotatory. Picrate: *m* 198–9; styphnate 179–82 (C.A. **35**, 7115[9]).

Stovaine: M.P. 175. Local anesthetic. S·HCl: 202; picrate: 110–12; styphnate: 120–2 (C.A. **35**, 7116[4]).

α-Estradiol: M.P. 176–8. Structure: 3,17-Dihydroxy-$\Delta^{1,3,5}$-estratriene. White crystals; $[\alpha]_D$ + 81 (in EtOH). Insol. H_2O; sol. org. solv. and oils. 3-Acetate: *m* 137; 17-acetate: 215–7.5; diacetate: 127; 3-benzoate: 194–5 (rapidly heated). When quickly cooled from 195 to 110 a form *m* 174–5 is obtained; 3,17-dibenzoate: 168–9. H_2SO_4 → orange color [Marrian, *Biochem. J.*, **24**, 435, 1021; Schwenk and Hildebrandt, *Naturwiss*, **21**, 177; *Biochem. J.*, **32**, 357].

Quinine: M.P. 177(172.8). Other M.P.: 176, 174.9, 173.5. Compd. with $3H_2O$: *m* 57. Usually the commercial form is $+2H_2O$ (lost at 125); $Q_2 \cdot H_2SO_4 \cdot 2H_2O$($H_2O$ lost at 100): 205; $Q \cdot H_2SO_4$: 160; Q·HCl: 158–60; Q·2HCl:

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(browns at 165–75) 180–5; Q·HBr: 200; acetate: 140; trichloroacetate: 139–40; (mono) citrate: 204*d*; (mono) salicylate: 195; acetylsalicylate: 157; acetyl: 116–7(108); benzoyl: 139; salicyloyl (saloquinine): 140; anisoyl: 87–8; cinnamoyl: 111. With conc. H_2SO_4 → green color, turning to red-brown or dull violet on warming; silicotungstic acid in 1% HCl ppts. even in 1 : 1,000,000 dilution. Acid $KMnO_4$ in cold → quitenine: *m* 286*d* and formic acid. Alk. $KMnO_4$ → pyridine-2,3,4-tricarboxylic acid: 250; CrO_3 → quininone: 108, and quininic acid: 280*d*. Boiling AcOH → quinicine: 60. For identification of quinine salts, see C.A. **32**, 1402[2]. For new reactions and differentiation from strychnine, see C.A. **26**, 3332. For picrate, *m* 131 and styphnate, *m* 149-50, see C.A. **35**, 7115.

Indican: M.P. 176–8 anhyd. (3H₂O: m 57–8). The formula of comp. is $C_{14}H_{17}O_6N$ and differs from the "indican" of urine ($C_8H_7O_4NS$, indoxylsulfuric acid, which is not stable in the free form but as the salt: $KC_8H_6O_4NS$ *d* 180). Pentaacetyl: (I) *m* 148; (II) *m* 112 [Robertson and Waters, *J. Chem. Soc.*, **1933**, 30]. For detection of urinary indican, see C.A. **27**, 2703[9]; or texts dealing with urinalysis.

Brucine: M.P. 178. $B \cdot 4H_2O$: *m* 105. Soln. of $HgNO_3$ reddens compd. on warming. HNO_3 → deep red color, which on evaporation → violet color with $SnCl_2$. $B \cdot HNO_3 \cdot 2H_2O$: 230*d*; picrolonate: 290d; pptd. by silicotungstic acid in presence of 1% HCl even in 1 : 500,000 dilution.

Michler's Ketone, 4,4′-Bis-(dimethylamino)-benzophenone: M.P. 179 (177, 174). Picrate: *m* 156 (Fehrmann, *Ber.*, 20, 2846); oxime: 233; phenylhydrazone: 174–5. For reduction to the Michler's hydrol, see C.A. **31**, 6212[8].

Styphnic acid (2,4,6-Trinitroresorcinol): M.P. 178–9(175.5). Compd. is explosive. Forms addn. compds. with many hydrocarbons. Dimethyl ether: *m* 124–5; aq. soln. gives ppt. with $Pb(OAc)_2$ but not immediately with ammoniacal $CuSO_4$ soln. (diffn. from picric acid). NaOH and $(NH_4)_2S$ soln. → yellow-red color (whereas picric acid gives blue-red).

Veratric acid: M.P. 181. Amide: *m* 164, sol. in hot H_2O; anilide: 150; anhydride: 124–5.

Corticosterone: M.P. 180–2(177–9). Sublimes at 190 under 0.01 mm. 21-Benzoyl: *m* 201–2; 21-acid succinyl: 194–5; 21-acetyl: 152–3; 21-butyryl: 170–1. Conc. H_2SO_4 → green fluorescence. Reduces $(NH_3)_2Ag$.

Phenothiazine (Thiodiphenylamine): M.P. 182 (180); B.P. 371. Sublimes. Alc. $FeCl_3$ → green color. Soln. of compd. boiled with Cu → carbazole. N-Acetyl: *m* 197.

Chlorophyll b: M.P. 183–5. Formula $C_{55}H_{70}O_6N_4Mg$; dark green powder. *a*-Form: *m* 150–3.

Auxin-B: M.P. 183. See Auxin-A: M.P. 196.

***cis*-Androsterone: M.P. 184–5(178, 182).** Acetyl: *m* 160–1; benzoate: 178; oxime: 215–6; semicarbazone: 276, phenylhydrazone: 153–4. For color reaction with *m*-dinitrobenzene, see Callow et al., *Bioch. J.*, **32**, 1312.

Thamnol: M.P. 186. Triacetyl: *m* 133; anil.: 128–9; phenylhydrazone: 194*d*; *p*-nitrophenylhydrazone: 320*d*.

α-Carotene: M.P. 187(172–4). Formula: ($C_{40}H_{56}$). Dark red plates or prisms. Isomerizes in soln. to neo-α-carotene. $SbCl_3$ in $CHCl_3$ → blue color. Oxidizes when exposed to air, whether crystalline or in solution [Escher, *Z. Physiol. Chem.*, **64**, 47], to a white amorphous product [Baumann and Steenbock, *J. Biol. Chem.*, **101**, 561].

Thiosemicarbazide-hydrochloride: M.P. 188. For derivatives, see Aldehydes and Ketones, page 249.

Nitron: M.P. 189*d*. Formula: $C_{20}H_{16}N_4$. Yellow leaflets or powder; insol. H_2O; sol. in many org. solv. Nitrate is insoluble (quantitative precipitant for nitrate ion); also the chlorate, perchlorate, thiocyanate, and other salts are difficultly soluble; alc. soln. turns red (decomposing) if not protected from light.

17-Equilenone II: M.P. 189. See Bachman and Wilde, *J. Am. Chem. Soc.*, **62**, 2084(1940).

Sulfaguanidine (Sulfanilguanidine): M.P. anh. 189–190. The compd. cryst. with $7H_2O$ and *m* 142.5–143.5. S·HCl: *m* 205–6; N_4-acetyl 262–6; see C.A. **34**, 7405, and **38**, 5360[6]; *Nature*, **148**, 24.

Sulfapyridine: M.P. 190–1 (191–2; 190–3). N_4-Acetyl: *m* 226–7(225); color reaction: C.A. **38**, 5360[6].

Glutathione: M.P. 190–2*d*. Phenylurethan: *m* 210 (foaming); heated with H_2O at 62 → glutimic acid (*m* 182–3) and cysteinylglycine. Addition of Cu_2O to soln. in 0.5 N H_2SO_4 → insol. cryst. Cu deriv.

Barbital (5,5-Diethylbarbituric acid; Veronal): M.P. 191; B.P. 245(260*d*). Forms addition compd. with hydroquinone: *m* 110; with quinine: 136. Ammoniacal $AgNO_3$ gives cryst. ppt. identified by microsublimation (phenobarbital gives no cryst. ppt.; see C.A. **34**, 856, and **32**, 306 and 2869; *J. Assoc. Official Agri. Chem.*, **20**, 553.) For other microchemical tests, see

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C.A. **37,** 3557, and **38,** 2454. Boiled with excess Na_2CO_3 or fused with NaOH, evolves NH_3. Gives white ppt. soluble in NH_3 with $Hg(NO_3)_2$ soln.

Vitamin C (*l*-Ascorbic acid): M.P. 190–2. $[\alpha]_D^{20}$ + 20 (1.4% soln.). Somewhat acid taste. Cryst. in white colorless plates, 1 g sol. in 3 ml of H_2O or 50 ml EtOH; insol. in Et_2O and C_6H_6. The most characteristic property is its strong reducing action in solution and its ease of oxidation catalyzed by Cu and Ag. Reduces methylene-blue in light to the leuco form. Phosphomolybdic acid in acid soln. → blue color. Molybdenum - phosphotungstic acid → violet [Bezssonoff, *Vitaminforsch*, **5,** 193]. Boiling with HCl acid forms furfural [Roe, *Science*, **80,** 561]. Titrated usually with 2,6-dichlorophenolindophenol [Marker and Lawson, *J. Am. Chem. Soc.*, **60,** 1334; Barnett and Reichstein, *Helv. Chim. Acta*, **21,** 926, and **22,** 75; Tillmans, *Z. Untersuch Lebensm.*, **54,** 33]. For detection, see also C.A. **33,** 1233; **37,** 4414; **36,** 3120 and 4536; and **34,** 7782.

Vitamin K (Phthiocol): M.P. 192(173). See Phthiocol: M.P. 173.

Bilirubin: M.P. 192.5. Formula $C_{33}H_{36}O_6N_4$. For detn., see C.A. **28,** 6753, and **31,** 7080; oxidation with CrO_3 → hematic acid. Gentle reduction → mesobilirubin ($C_{33}H_{40}O_6N_4$) further reducible to urobilinogen, which can be detected by intense color with Ehrlich's *p*-dimethylaminobenzaldehyde reagent, and which under the action of air and light is transformed into a yellow pigment urobilin (or stercobilin).

Biuret: M.P. 193*d*(190*d*). Compd. heated → cyanuric acid (which decomposes to cyanic acid without melting) and NH_3. With very dilute $CuSO_4$ in KOH soln. → violet (Biuret reaction). Acetyl: *m* 193.

Thebaine (Paramorphine): M.P. 193. Diacetyl: *m* 231–2. For identification, see C.A. **38,** 3087.

Chrysazin (1,8-Dihydroxyanthraquinone): M.P. 193. Diacetyl deriv.: *m* 231–2; monomethyl ether: 197–8. Reduction with HI and P → anthranol: *m* 177.

Calcium pantothenate: M.P. 195–6. Pantothenic acid (Vitamin B_3, $C_9H_{17}O_5N$). Readily sol. in H_2O, EtOAc, dioxane: pale yellow viscous oil, $[\alpha]_D^{25}$ + 37.5. No specific tests or deriv. are known. Ca salt, microcrystalline: $[\alpha]_D^{20}$ + 24.3, *m* 195–6. The vitamin forms an acetyl derivative which can be distilled at 10^{-5} mm [Woolley et al., *J. Biol. Chem.*, **125,** 715].

Auxin-A: M.P. 196. $[\alpha]_D$ − 3.19 (in EtOH). Monobasic acid $C_{18}H_{32}O_5$ [Kogl et al., *Z. Physiol. Chem.*, **216,** 31; **220,** 137]. Lactone: *m* 173; *p*-phenylphenacyl: 166: tri-m-dinitrobenzoyl: 168; methyl ester: 150. Auxin-B differs in M.P. and in being insol. in ether, also in its greater resistance to oxidation, which with both A and B yields α,α'-d-*sec*-butylglutaric acid. Auxin B: 183, $[\alpha]_D^{20}$ − 2 8. *p*-Phenylphenacyl: 174; semicarbazone: 176.

Cholic acid: M.P. 199–201(198). Formula: $C_{24}H_{40}O_5$. Dehydrated at 100–110. Methyl ester: *m* 162; ethyl ester: 127; 3,7-diacetyl: 257. Gives blue compd. with I_2 soln. $(C_{20}H_{40}O_5I)_4KI + 2H_2O$ [Mylius, *Z. Physiol. Chem.*, **11,** 30, Villa, *Bull. Soc. Chim.*, (4) **13,** 866].

Guanidine carbonate: M.P. 197. The base forms colorless, deliq., caustic crystals, which readily take up CO_2 from the air: other salts are: G·HCl, white cryst.; G·HNO_3: *m* 214; acetate: 229–30; picrate: 333; 1-N-acetyl: 145; N-benzenesulfonyl: 212 (its picrate: 190–1).

Cupreine (Hydroxycinchonine): M.P. 198. Compd. loses $2H_2O$ at 120. $C_2 \cdot H_2SO_4 \cdot 6H_2O$: *m* 257*d*; diacetyl: 88.

Xylan: M.P. 198. Hydrolysis by 3% HNO_3 → xylose and arabinose. Dimethyl ether: 194–6 (198); stearate: 48; benzyl ether: 158–9 [C.A. **29,** 5418; **25,** 4855].

Quinizarin (1,4-Dihydroxyanthraquinone): M.P. 200–2(194). Subl. with partial carbonization [Grimm, *Ber.*, **6,** 508]. No authority could be found for M.P. 280 given in *Hackh's Chemical Dictionary*. *Org. Syntheses*, Coll. Vol. I (2nd Ed.), p. 477, gives the M.P. 200–2; others give it as 198, 194, or thereabouts; acc. to Lindpainter [*Mikrochemie*, **27,** 21–41] quinizatin is enantiotropic, existing in two modifications: (I) orange: *m* 195; (II) red: *m* 201. Is pptd. from dil. KOH soln. by CO_2 (diffn. and sepn. from purpurin, Achunck and Roemer, *Ber.*, **10,** 555). Alk. $K_3Fe(CN)_6$ → phthalic acid [Dralle, *Ber.*, **17,** 376]; heated with MnO_2 and H_2SO_4 to 140 → purpurin [Baeyer and Caro, *Ber.*, **8,** 152]. PbO_2 in AcOH at 20 gives 1,4,9,10-anthradiquinone: *m* 211–13*d* [Dimroth and Schultze, *Ann.*, **411,** 346].

Sulfathiazole: M.P. 202.5. S·HCl: *m* 193–7; Na-deriv.: 265; N_4-acetyl: 256–7. For color reactions, see C.A. **38,** 5360.

Isatin: M.P. 203.5. Phenylhydrazone (yellow): *m* 210 [*J. Soc. Chem. Ind.*, **50,** 64 T].

Aconitine: M.P. 204(197–8). Taste burning: very poisonous. Dextrorotatory: $[\alpha]_D$ + 17.3 (in $CHCl_3$), but its salts are levorotatory. A·HCl: *m* 170–2*d*; A·HBr: 176–80; A·$HAuCl_4$: 157–8 (air dried: 136); dried at 100: 151–2, from

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Me_2CO: 138–40. Picrate: 100–2. For detection and identification, see C.A. **35**, 5819, 7115, 5645; **26**, 1, 894, 3874, 5382.

l-Ecogonine: M.P. 205. Compd. with $1H_2O$: *m* 198d. Amide: 198: benzoyl: 195; E·HCl: 246; $E_2 \cdot H_2PtCl_6$: 226.

Veratrine (Cevadine): M.P. 205*d*(180, 150–5). Sternutatory (sneeze-producing). Benzoyl: *m* 255 (170–180); *o*-nitrobenzoyl: 236; V·$HgCl_2$·HCl silvery plates: 172*d*; phosphotungstic acid in presence of 1% HCl acid gives a ppt. even in 1 : 100,000 dilution. Soln. in conc. HCl becomes violet, changing to red on boiling.

Chrysarobin: M.P. 205–10(170–8). For discussion of structure, etc., see Jowett and Potter, *J. Chem. Soc.*, **81**, 1578; Tutin and Clewer, *ibid.*, **101**, 290. Chrysarobin, formerly thought to be a pure substance, is now known to consist of several compd., of which chrysophanol-anthranol, $C_{15}H_{12}O_3$, is the most important; compd. *m* 202. Deriv. diacetyl: *m* 193; triacetyl, *m* 238. Present in chrysarobin as the monomethyl ether.

Cinchonidine: M.P. 207.2(202.4). Large trimetric prisms $[\alpha]_D^{20} - 111$; levorotatory isomer of cinchonine (*m* 264). C·HCl·$2H_2O$: *m* 242*d*. Cinchonidine is disting. from quinine and quinidine in that its salts are non-fluorescent in soln., from cinchonine in that in aq. soln. its sulfate gives a white ppt. with sodium tartrate. Acetyl deriv.: *m* 47–9; benzoyl: 183; benzenesulfonyl: 166. Picrate: 208–9 (190–3).

l-Adrenaline (Epinephrine; Suprarenine): M.P. 211–2*d*. Rapidly heated: *m* 215. A·HCl: 157 $FeCl_3$ → green color, which Na_2CO_3 changes to red. For oxidation to red color, sensitive to 1 : 300,000 dilution, see Frankel and Allers, *Biochem. Z.*, **18**, 40; also C.A. **37**, 2883.

Dialuric acid (5-Hydroxybarbituric acid): M.P. 214–5*d*. Compd. with NH_3 → uramil, which does not melt below 400 (C.A. **33**, 1671[6]). Na and K salts sparingly sol. hot H_2O. Acetyl: *m* 210–2; benzoyl: 209–10. For ident. of micro qu., see C.A. **36**, 2235[8].

Purine: M.P. 216–7. Very stable to oxidizing agents. P·HNO_3: *m* 205*d*; picrate: 208.

Cantharidin: M.P. 218(205, 212). Compd. is a dicarboxylic anhydride ($C_{10}H_{12}O_4$). Phenylhydrazone: *m* 238. For detection, see C.A. **11**, 1880[9]; **21**, 1328[2]; **18**, 2784[3].

Hydantoin (Glycollylurea): M.P. 218(220, 216). Compd. with HNO_3 → 5-nitrohydantoin: *m* 170*d*; 1,3-diacetyl: 104–5, boiled with water gives 1-acetyl: 143–4; 1,3-dichlorohydantoin (formed by Cl_2 action on aq. soln.): 120–1. With 3,5-dinitrobenzoic acid in alk. soln. hydantoin gives a purplish rose color [Benedict and Behre, *J. Biol. Chem.*, **114**, 515].

β-Estradiol: M.P. 223. $[\alpha]_D^{18} + 56.7$ (in EtOH); 3-methyl ether: *m* 109–10; 3,17-diacetate: 139–41.5; 3-benzoate: 156–7.

Digitalin: M.P. 229(210–17). Dec. 235; hydrolysis → digitaligenin and digitalose and glucose.

Allantoin: M.P. 230–6. 1-Acetyl: *m* 236*d*; 1,3-diacetyl: 247*d*.

Vitamin H (Biotin $C_{10}H_{16}O_3N_2S$): M.P. 230–2. $[\alpha]_D^{22} + 92$ (in 0.1 *N* NaOH); sol. H_2O, EtOH, insol. Et_2O, $CHCl_3$. Methyl ester: *m* 166–7 See Harris et al., *Science*, **97**, 447, and Hofmann et al., *J. Am. Chem. Soc.*, **63**, 3237.

Insulin: M.P. 233. A protein hormone. For prep.: Romans et al., *Ind. Eng. Chem.*, **32**, 908. Prep. of picrate: Dudley, *Biochem. J.*, **17**, 376–90; **18**, 147. For other details, see *Insulin* by Hill and Howitt (London, Hutchinson Scientific Publications, 1936); *Insulin*, by Jensen (Commonwealth Publications, New York, 1938).

d-Quercitol: M.P. 234(228–30, 235–7). Compd. with HNO_3 → mucic acid; pentacarbanilate: *m* 120–40.

Phthalimide: M.P. 234(238, 228). N-Acetyl: *m* 133–5; N-chloro-: 183–5; N-bromo-: 206–7; N-cinnamyl: 153–7; N-xanthyl: 176–7.

Pregnanediol: M.P. 234. 20-Acetyl: *m* 170.5; diacetyl: *m* 180.

Digitonin: M.P. 235. Formula: $C_{55}H_{92}O_{29}$. One of the few well-characterized saponins; occurs in digitalis purpurea, but is difficult to isolate in the pure state. Separated from other saponins by fractional ppn. with AmOH [*Ber.*, **43**, 3562, and **49**, 701]. Hydrolysis → glucose (2 mols.), galactose (2 mols.), and digitogenin (a steroid $C_{27}H_{44}O_5$: *m* 253). Used as a precipitant for cholesterol, and also for sterols in butter (*Analyst*, **48**, 155; **54**, 735).

Caffeine: M.P. 236.8(234–5). Sublimes at 178. Crystallizes from water with $1H_2O$, which it loses on exposure to air; C·HCl·$2H_2O$: *m* 80–100*d*. Gives the murexide reaction; pptd. by $PdCl_2$ (as are also theophylline, pyridine, etc.); see Guilland and Macrae, *J. Chem. Soc.*, **1932**, 2231–6. For identification, see C.A. **37**, 3897, and **36**, 217.

Nicotinic acid (Niacin): M.P. 237(228, 232). Sol. in H_2O (20 mg/ml) but insol. in Et_2O. Sublimes without decompn. Amide: *m* 129 (see Nicotinamide), dissolves in org. solvents (separation from the acid). Warmed in solution with CNBr in the dark and treated with an amine (p-amino-acetophenone gives quantitative test) → yellowish green color which can be extracted with amyl alcohol [Bandier and Hald, *Biochem. J.*, **33**, 264 (1939)]. Some other pyridine derivatives, such as trigonalline and nicotine, give similar color.

Equilin: M.P. 238–40. Formula: $C_{18}H_{20}O_2$; structure· 3-hydroxy-17-keto-$\Delta^{1,3,5,7}$-estratetraene.

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$[\alpha]_D + 308$ (in dioxane); benzoate: *m* 197–8; methyl ether: 161.

Ninhydrin (Triketohydrindene hydrate): M.P. 241–3*d*. Becomes anhydrous at 128–30. Oximes have been made indirectly. Amino acids, even in traces, give a deep blue coloration [Ruhemann, *J. Chem. Soc.*, **97**, 2025, and **99**, 793, 1486].

Urazole: M.P. 244(240). Acetyl: *m* 221.5; diacetyl: 206; triacetyl: 138. For further details, see C.A. **24**, 1114[8].

Barbituric acid (Malonylurea): M.P. 245*d*. Forms a red compd. with picric acid and NaOH [Greenwald, *J. Am. Chem. Soc.*, **50**, 1469]. Dibromo: *m* 235*d*; phenylhydrazone: 284.

Melamine: M.P. 250*d*. Structure: 2,4,6-triamino-*s*-triazine. Picrate: 268*d* [Krall, *J. Chem. Soc.*, **103**, 1385].

Vitamin B_1 (Thiamine chloride-hydrochloride; Aneurin: $C_{12}H_{17}ON_4SCl \cdot HCl$): M.P. 250*d*(245–8*d*, 241–4, 233–4). Cryst. with ½ mol H_2O from aq. alcohol. Compd. has two M.P.: 246–250 and 232–4, due to dimorphism. Very sol. in H_2O, very sl. sol. in EtOH. Bromide-hydrobromide: 229–31; nitrate: 164–5; sulfate (a): 203; (b): 276–8 (dimorphous); benzoyl chloride does not react; picrolonate (a): 165; (b): 229 (dimorph.); picrate: 208 (yellow-ppt.). Alk. diazotate of *p*-aminoacetanilide → red purple ppt., sol. in isobutyl alcohol [Pfiffner and North, *J. Biol. Chem.*, **132**, 461, and **134**, 781; Prebluda and McCollum, *ibid.*, **127**, 495]. Reaction with NaN_3 and I_2, sensitive to 0.2 microgram of thiamine [Feigl and Ribeiro, C.A. **37**, 1732]. Identified by ppn. with Reinecke's salt and by the thiochrome fluorescence reaction [Mikkelsen, C.A. **37**, 6411; *Arch. Pharm. Chem.*, **49**, 303–6]. For complete inform., see *Thiamin*, by Williams and Spies (Macmillan, N. Y., 1938).

Prontosil: M.P. 247–51. Bactericide; sol. in 400 parts H_2O. Red crystalline powder. Structure: 4′-sulfamino-2,4-diamino-azobenzene hydrochloride [C.A. **30**, 766[2], 4563[8]]. Color reaction with NaOCl: C.A. **38**, 5360[6].

Hesperidin (Vitamin P): M.P. 251–2(254*d*). Formula: $C_{28}H_{34}O_{15} \cdot Ba(OH)_2$ → isoferulic acid: *m* 228(222); diacetyl: 142–3.

Digitoxigenin: M.P. 253. $[\alpha]_D + 19.1$ in EtOH. 3-Monoacetyl: *m* 217.

Morphine: M.P. 254*d*(230). $[\alpha]_D^{23} - 130.9$ in MeOH. $M \cdot HCl \cdot 3H_2O$: *m* 200; acetate: 200*d*; phenylurethan: 127–30; phenolsulfonyl: 165. Picrate: 228; styphnate: 201–2. Gives ppt. with most alkaloid reagents: KI, phosphomolybdic acid, picric acid, etc. A soln. of 1 drop of formalin in 1 ml of H_2SO_4 gives purple color changing to blue. Conc. HNO_3 → blood red color. For other color reactions, see C.A. **13**, 2252[9]; **31**, 8118[3]; **38**, 3088[1]; and **35**, 5819[8].

Cinchonine: M.P. 254(268.8); B.P. 448. Begins to sublime at 220. The M.P. is given as 264.3 [Jungfleisch and Leger, *Compt. rend.*, **132**, 830], as 255.4 [Lenz, *Z. Anal. Chem.*, **27**, 572); the M.P. 268.8 is that det'd by Skraup [*Ann.*, **197**, 355], while the M.P. 254 is that by Buttle et al. [*Biochem. J.*, **28**, 437]. Does not form a sol. tartrate (diffn. from cinchonidine). $KMnO_4$ in cooled dil. H_2SO_4 → cinchotenine: *m* 197–8. $C \cdot H_2SO_4 \cdot 2H_2O$: 200*d*; O-acetyl: 51–3; O-benzoyl: 106–7; O-*p*-toluenesulfonyl: 173; picrate: 193–4; styphnate: 106; $C \cdot HCl\ 2H_2O$: 217–8*d*. Reaction with Marme's reagent, see C.A. **37**, 3881[4].

Sulfadiazine (Sulfapyrimidine, N-2-Pyrimidylsulfanilamide) M.P. 255–6*d*. Bactericide like sulfanilamide. N_4-Acetyl: *m* 258–9. For detection, see C.A. **38**, 5360; Robin et al., *J. Am. Chem. Soc.*, **64**, 568.

Digitoxin: M.P. 255–6. $[\alpha]_D^{20} + 4.8$ (in dioxane). Acid hydrolysis → digitoxigenin: *m* 253, and digitoxose: 108–9 *q.v.* Gives the Keller-Killian reaction with $FeCl_3$ [*Arch. Pharm.*, **234**, 273].

Equilenin: M.P. 258–9. Structure: 3-hydroxy-17-keto-$\Delta^{1,3,5,6,8}$-estrapentaene. $[\alpha]_D + 87$ in dioxane. Acetate: *m* 156–7; benzoate: 222–3; methyl ether: 197–8.

Estrone: M.P. 259. Structure: 3-hydroxy-17-keto-$\Delta^{1,3,5}$-estratriene [Adam et al., *Nature*, **132**, 205]. Occurs in 3 polymorphic forms: *m* 254, 256, and 259. Distils undecompd. at 150–200/0.002 mm. H_2SO_4 → orange color, fluorescing green [Marrian, *Biochem. J.*, **24**, 435, and 1021; Schwenk and Hildebrandt, *Naturwiss*, **21**, 177; *Biochem. J.*, **32**, 357]. Acetyl: 126; benzoyl: 218–9; oxime: 241–2; semicarbazone: 266–7; methyl ether: 167.5–169.5. For identification with *m*-dinitrobenzoic acid and KOH in EtOH, see Steiger and Reichstein, *Helv. Chim. Acta*, **21**, 828; for identification by diazotization and dianisidine, see Hoehm and Mason, *J. Am. Chem. Soc.*, **60**, 1493.

Pentaerythritol: M.P. 260(258–60, 253). Compd. with HNO_3 → oxalic acid; with CrO_3 → HCOOH and CO_2. Deriv. tetra-acetate: *m* 82–3; tetranitrate: 138–40.

Acenaphthenequinone: M.P. 261. $K_2Cr_2O_7$ in AcOH → naphthalic acid: *m* 274. Dioxime: *m* 192–3; monoxime in 2 forms: (I) *m* 230, (II) *m* 207; disemicarbazone: 271; monophenylhydrazone: 179.

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Triphenylacetic acid: M.P. 267. Anhydride: *m* 163; amide: 246–7 (238); anilide: 174; N-benzoyl: 185–6.

Cinchonine: M.P. 268.8(254). See Cinchonine. M.P. 254.

Perylene ($C_{10}H_{22}$): M.P. 274(266). The M.P. 274 agrees with that (273–4) found by Morgan and Mitchell [*J. Chem. Soc.*, **1934**, 536] for perylene deprived of impurities (by regeneration from picrate); Calcott, Tinker, and Weinmayr [*J. Am. Chem. Soc.*, **61**, 950], nevertheless, give the M.P. of perylene prepared by two different methods as 266; for prep. and ident., see the foregoing citations. Monopicrate: *m* 221; dipicrate: 154–5 [Brass and Tengler, *Ber.*, **64**, 1650].

Theophylline: M.P. 274(264–5, 269–72). Acc. to Doser [*Arch. Pharm.*, **281**, 251–6] the stable form *m* 274, an unstable one at 271; Grinberg gives the M.P. as 264–5 [C.A. **35**, 3974], which agrees with that found by Yoshitomi [C.A. **19**, 2303], who gives it as 264, the same as Kossel [*Z. Physiol. Chem.*, **13**, 302; *Ber.*, **21**, 2166]; but Eichengrun [*Chem. Zentr.*, **1902 II**, 1387] reported 268. 7-N-Acetyl: 158; 7-N-benzoyl: 202. For new color reactions, see Sanchez, C.A. **38**, 2289 (diffn. from caffeine and theobromine). Compd. with phenobarbital: 195–6. Higgins and Dunker, *J. Am. Pharm. Assoc.*, **33**, 310–14; methylation by warming in MeOH with KOH and CH_3I converts it into caffeine: *m* 235.

Flavazole: M.P. 274–5. For formula and prepn., see C.A. **37**, 5066–8; Ohle and Iltgen, *Ber.*, **76**, 1–14; C.A. **38**, 1236; *Ber.*, **75**, 1536–40. Sublimes below M.P. 1-Methyl deriv.: *m* 165.

Isocytosine: M.P. 275–6*d*. See Cytosine: M.P. 308.

Estriol: M.P. 281. Structure: 3,16,17-trihydroxy-$\Delta^{1,3,5}$-estratriene. $[\alpha]_D + 61$ (in EtOH). Compd. with $H_2SO_4 \rightarrow$ orange coloration [Marrian, *Biochem. J.*, **24**, 435, 1021], fluorescing green [Schwenk and Hildebrandt, *Naturwiss*, **21**, 177; *Biochem. J.*, **32**, 357]. Triacetate: *m* 126; methyl ether: 162–4.

Vitamin B_2 (Riboflavin; Lactoflavin; Vitamin G): M.P. 282*d*(275–80). Darkens at 240. Light slowly destroys it. Orange yellow cryst. needles, insoluble in fat solvents, and only sl. sol. in H_2O (in 9000 parts at 25), very sol. dil. NaOH. Its most characteristic feature is its intense yellowish green fluorescence. Readily hydrogenated to dihydro compd., colorless, nonfluorescent, leuco-riboflavin. Resists acids, Br_2, H_2O_2, HNO_3. Forms a tetra-acetate on acetylation [Kuhn and Wagner-Jauregg, *Ber.*, **66**, 1577, 1950]. For detection, see C.A. **38**, 1005.

Estriol: M.P. 283(275). $[\alpha]_D + 34.4$ in pyr. Heated in vac. with $KHSO_4 \rightarrow$ estrone (*m* 259), *q.v.* Methyl ether (formed with diazomethane): 162.5–4; triacetyl: 127.

Chloranilic acid: M.P. 283–4. Compd. cryst. in reddish leaflets with 2 mol. H_2O. Hot H_2O dissolves to a violet soln. Reacts strongly acid. Diacetyl: 182.5. Dimethyl ether: 141–2.

Strychnine: M.P. 286–8(268). Melts at 270–1 when slowly heated. Boils at 270 under 5 mm. $[\alpha]_D^{18} - 139.3$ in $CHCl_3$, -104.5 in abs. EtOH Almost insol. in cold H_2O, Et_2O, etc. Warmed in dil. HNO_3 and $K_2Cr_2O_7 \rightarrow$ intense scarlet coloration. H_2SO_4 and HNO_3 (1 drop) and a little $K_2Cr_2O_7$ (or other strong oxidizing agent) $\rightarrow$ violet-blue $\rightarrow$ red $\rightarrow$ yellow coloration. Deriv. $S_2 \cdot H_2SO_4$ (anh.): *m* 200; monopicrate: 270*d*; monopicrolonate: 290*d*; *d*-tartrate: 228; benzylidene deriv.: 235–7. A characteristic reaction (sensitive 1 microgram): amm. metavanadate and $H_2SO_4 \cdot 2H_2O$ colors it a magnificent violet, then red, and finally orange [Mandelin, *Z. Anal. Chem.*, **25**, 240]. For a new highly sensitive test, see Martini, C.A. **38**, 530.

Chloranil: M.P. 290(285). Sublimes without melting if carefully heated, but melts at 290 in a sealed tube. Stable to oxidizing agents, being one itself. SO_2, or HI and P $\rightarrow$ tetrachlorohydroquinone (*m* 232), whose dibenzoyl deriv. *m* 232.

Alizarin (1,2-Dihydroxyanthraquinone): M.P. 290; B.P. 430. Orange or red crystals; alk. soln. is purple. $HNO_3 \rightarrow$ phthalic acid. H_2SO_4 and $MnO_2 \rightarrow$ purpurin. Zn dust $\rightarrow$ anthracene. Deriv.: 2-acetyl: *m* 205 (198–201); diacetyl: 184 (180); 2-benzoyl: 214–6; dibenzoyl: 187 (an unstable form *m* 160); 2-phenylacetyl: 165; 2-*p*-bromobenzoyl: 195; dibenzenesulfonyl: 183. $Ca(OH)_2$ or $Ba(OH)_2$ ppts. blue salts from alk. solns.

Betaine: M.P. 293. Becomes anhydrous at 100. Colorless, deliq. crystals with sweet taste. Isomerizes at M.P. to methyl ester of dimethylglycine (which ester is a liquid: *b* 135). Conc. KOH soln. $\rightarrow$ trimethylamine. B·HCl (known also as "acidol"): *m* 227–8*d*; B·HBr 233*d*; B·HI: 200 (188–9); $B \cdot HAuCl_4$: plates: 200–9, rhombohedra: 248–50*d* (230–5); picrate: 183.

Diphenylhydantoin: M.P. 295–8(292–7). The M.P. is also given as 286 corrected. Monoacetate: *m* 215–7 [*Ber.*, **41**, 1379 (1908); *ibid.*, **44**, 411 (1911)].

Creatine: M.P. 303(295). See also Creatinine:

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M.P. 305. Faintly bitter taste, irritating the pharynx; forms addn. compd. with $ZnCl_2$, decompd. into its constituents by hot water [Neubauer, *Ann.*, **137**, 300]. N-Diacetyl: *m* 165 [Erlenmeyer, *Ann.*, **284**, 50]. Picrate: 218–20. Sl. alk. soln. with a few drops of fresh 1% soln. of biacetyl gives a pink color (slowly in the cold, rapidly when heated); this reaction differentiates it from creatinine [Harden and Norris, *J. Physiology*, **42**, 333]. For detection, see C.A. **19**, 663; *Compt. rend.*, **38**, 839; *Ann.*, **92**, 407. Compd. with mineral acids → creatinine; $Ba(OH)_2$ → urea and sarcosine.

Creatinine: M.P. 305. Taste somewhat caustic, decidedly bitter. C·HCl: *m* 230–40*d* [Korndorfer, *Arch. Pharm.*, **242**, 636]; C·HI: 195 (extremely sol. in H_2O and EtOH); C·$HAuCl_4$ (anh.): 182–5 (yellow leaflets); (mono) picrate: 220 [*Org. Syntheses*, Coll. Vol. I, 2nd Ed., p. 173]; also given as 212 and 240 [Worner, *Z. Physiol. Chem.*, **27**, 7], and 220–1*d* [King, *J. Chem. Soc.*, **1930**, 2377]; dipicrate: 161–6. Compd. with aq. soln. of Mg salt of dipicrylamine gives very insol. red ppt.: 165–7 [C.A. **38**, 2897]. Mono benzoyl: 190 (from benzoic anhydride or benzoyl chloride) [Greenwald, *J. Am. Chem. Soc.*, **47**, 1443–47]; tribenzoyl; 238–40 (*ibid.*); flavianate ($C_4H_7ON_3 \cdot C_{10}H_6O_8N_2S$) dec. 250 [Kossel and Gross, *Z. Physiol. Chem.* **135**, 167–74]; tartrate: 207–9 [Poulsson, *Arch. Exp. Path. Pharmacol.*, **51**, 227–38]; Reineckate: 175. For oxime and other salts, see monograph of Hunter, *Creatine and Creatinine* (Longmans, Green and Co., New York, 1928), pp. 38–52. For color reactions: *ibid.*, pp. 24–28. For an extensive review of the literature on creatine and creatinine, see Shiver, *Chem. Reviews*, **6**, 419–44.

Cytosine: M.P. 308*d*. See Hilbert et al., *J. Am. Chem. Soc.*, **57**, 554; see also Cytosine: M.P. 320.

2,5-Piperazinedione ("Glycine anhydride"): M.P. 311–2*d*. Sublimes at 260; P·HCl: *m* 129–30; di-α-naphthylurethan: 232*d* [*J. Am. Chem. Soc.*, **51**, 3078].

β-Fluorescein: M.P. 314–6. Occurs in two forms, both *m* 314–6*d* (sealed tube). Sublimes under 15–18 mm pressure as greenish-red crystals [Scharwin and Kusnezow, *Ber.*, **36**, 2023]; (I) yellow amorphous, crystallizes on heating at 250–260 or by boiling with dil. HCl → (II) the red form: stable red cryst. form with green iridescence. Decomp. when heated at 290 under atm. pr. Dil. alk. soln. shows an intense yellowish-green fluorescence, visible even in 1 : 40,000,000 dilution; it loses its fluorescence between *p*H 4.3 and 3.8. Heated with Zn dust in alk. soln. → fluorescin (*m* 125–7), *q.v.* Acetylation with AcOCl or Ac_2O → diacetate: *m* 205–6 (203–5) [Torrey and Brewster, *J. Am. Chem. Soc.*, **30**, 863; von Liebig, *J. Prakt. Chem.* (2) **85**, 267; McKenna and Sowa, *J. Am. Chem. Soc.*, **60**, 124]; benzoyl chloride → dibenzoate: 216–7 [Meyer, *Ber.*, **28**, 2963; Baeyer, *Ann.*, **183**, 14]; bis-phenylurethan: 195*d*; *p*-toluene sulfonate: 163–5. α-Fluorescein (made from commercial fluorescein): *m* 347 [von Liebig, *J. Prakt Chem.* (2) **85**, 258]; γ-fluorescein: yellow powder [*ibid.*, p. 263]; γ-fluorescein (made from disodium salt of ordinary fluorescein, heated at 300–350); does not melt up to 350 [*ibid.*, p. 264].

Quercetin (3,5,7,3′,4′-pentahydroxyflavone): M.P. 318–9(313–4). Compd. and H_2SO_4 → yellow soln. with faint green fluorescence. Reduces $NH_4 \cdot AgNO_3$ in the cold and Fehling's on heating. 3,7,3′,4′-Tetraacetyl: *m* 193–4; pentaacetyl: 193.5(190–1); pentabenzoyl: 188–90; pentachloroacetyl: 180.

Cytosine: M.P. 320–5. Compd. with HNO_2 → uracil: *m* 335; picrate: 265–6*d*. For color reactions, see Johnson and Clapp, *J. Biol. Chem.*, **5**, 163.

Benzidine sulfone: M.P. 327–8(350). Diacetyl deriv.: *m* 382 3; dibenzoyl: 384–5. For other information, see C.A. **25**, 4254[1]; *Ber.*, **22**, 2467.

Taurine (2-Aminoethanesulfonic acid): M.P. 328–9. The M.P. is uncorrected and was determined on the Maquenne block by Rumpf [*Bull. Soc. Chim.* (5) **5**, 878], who prepared it by several different methods. Heated in alk. soln. with a little *p*-nitrobenzoyl chloride, it gives no color reaction (diffn. from other amino acids) [Waser and Brauchli, *Helv. Chim. Acta.*, **7**, 740–58]; gives intense color with ninhydrin [Neuberg, *Biochem. Z.*, **56**, 502]. N-Acetyltaurine Na salt (made by action of Ac_2O on taurine in presence of NaOH): *m* 233–4; very hydroscopic; acidification gives no free acetyltaurine but only taurine [Teraoka, *Z. Thysiol. Chem.*, **145**, 238 43].

Uracil (2,6-Dihydroxypyrimidine): M.P. 338. Melts at 335 if slowly heated. Pptd. by $HgSO_4$ and $AgNO_3$, not by phosphotungstic acid or picric acid (diffn. from cytosine). Reactions: mostly those of cytosine (*m* 320–5). See C.A. **37**, 5338[1].

Theobromine: M.P. 337. (See also Caffeine: *m* 237). Sublimes at 290, but *m* 337 (329) in sealed tube. Gives murexide reaction. CrO_3 → methylparabanic acid: *m* 153–4. Methyla-

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tion (see theophylline: *m* 274) → caffeine (237); perchlorate H_2O: 271–3*d*; T·HCl and $AuCl_3$: 243; Hg salt: 310 (darkens at 295–305); T·$HgNO_3$: does not melt below 300; methochloride: 320–40*d*. Forms a gel with $AgNO_3$, which is characteristic of theobromine and differentiates it from caffeine; detects 0.01 g in 10 ml of liquid (which is thereby solidified): 0.05 g theobromine, 3 ml H_2O, and 6 ml NaOH soln. are let stand to clarify; after adding NH_4OH and 10% $AgNO_3$ (1 ml of each) and shaking, a solid colorless mass filled with air bubbles results, which when warmed to 90 melts, and on cooling again solidifies. Benzoyl deriv.: *m* 206; acetyl: 165; 8-chloroderiv. (formed by Cl_2 in $CHCl_3$ suspension of theobromine): 296–7.

Acridone: M.P. 354. *Org. Syntheses*, Coll. Vol. II (p. 16) gives M.P. as 348–52. EtOH soln. fluoresces blue. Zn dust → acridine: *m* 111. PCl_5 → 5-chloroacridine: 120 (also sublimes), which boiling H_2O reconverts to acridone.

Guanine: M.P. 360*d*. Crystallizes with 3 mol. of H_2O. Sublimes at 220 without decompn.; gives the murexide reaction. Benzoyl: *m* 234.

Xanthine: M.P. 360. Crystallizes with 1 mol. H_2O (lost at 130). Cannot be esterified. Heated decomposes into CO_2, NH_3, HCN, and $(CN)_2$. Phenol and NaOCl soln. → olive-green coloration [Thomas, *Bull. Soc. Chim.*, (4) **11**, 798]; perchlorate: sinters at 255, *m* 262–4*d*.

Adenine: M.P. 360–5*d*. Water of cryst. is lost at 110. $FeCl_3$ → red coloration. Diazobenzenesulfonic acid and alkali → red coloration. Heated on water bath half an hour with Zn and HCl, then diluted and saturated with NaOH, the liquid turns first red and later brownish red [Kossel, *Z. Physiol. Chem.*, **12**, 241]; picrate: *m* 279–81*d*.

Anthrapurpurin: M.P. 369 (subl. 170). 2-Acetyl: *m* 296–8; 2-benzoyl: 272–3; 1-methyl ether: 299–300; 2-methyl ether: 308.

Indigotin: M.P. 392 subl. Insol. in H_2O, EtOH, Et_2O; sol. in hot $CHCl_3$, hot $C_6H_5NH_2$. Reduced to indigo white with Zn and NaOH soln. Oxidized to isatin: *m* 201.

Uric acid: M.P. 400*d*. *D* 1.855 to 1.893. Dec. above 400 without melting and evolves HCN; gives the murexide reaction. Phosphomolybdic acid and dil. KOH → dark blue metallic ppt. which dissolves in mineral acids with a deep blue color. Oxidation with HNO_3 → alloxan: *m* 170*d*.

Uramil (5-Aminobarbituric acid): M.P. 400. For prep. etc., see *Org. Syntheses*, Coll. Vol. II. For color reaction, see Knott, *J. Soc. Chem. Ind.*, **60**, 313–4 T.

Indanthrene (anthraquinone-dihydroazine): Decomposes at 470–500. Dissolves in $C_6H_5NO_2$ and $C_6H_5NH_2$ with greenish-blue color. Strong HCl up to 400° is without effect. NaOCl oxidizes compd. to a yellowish-green azine reconvertible by direct sunlight or $NaHSO_3$. Distillation with P and HI or Zn dust → anthrazine: subl. 340. [Scholl, *Ber.*, **36**, 3429, and **40**, 924].

Phthalocyanine. Sublimes undecomposed under reduced pressure as bluish-green vapor at 550°, without melting. Distillation with soda-lime → benzonitrile (*b* 190.2) and NH_3. Converted to phthalimide (*m* 234) by HNO_3. Forms stable salts with Fe, Co, Ni, and Cu [Linstead, *J. Chem. Soc.*, **1934**, 1014; *Ber.*, **72**, 93].

Appendix

Appendix

I. Suggested List of Apparatus for Semimicro Qualitative Organic Analysis[1]

Locker Equipment (Returnable)	
2 Beakers, Pyrex	25 ml
2 Beakers, Pyrex	50 ml
2 Beakers, Pyrex	150 ml
2 Beakers, Pyrex	250 ml
1 Beaker, Pyrex	400 ml
1 Calcium chloride tube Sm	
2 Condensers Sm	
2 Distilling tubes (Sm pear-shaped preferred)	10 ml
2 Distilling tubes Sm	25 ml
1 Distilling tube Claisen Sm	25 ml
1 Cylinder graduated	10 ml
1 Desiccator bottle	60 ml
1 Evaporating Dish	30 ml
2 Flasks, Erlenmeyer	25 ml
1 Flask, pear-shaped	5 ml
1 Flask, pear-shaped	10 ml
1 Flask, pear-shaped	25 ml
2 Funnels with etched band	50 mm
1 Funnel, separatory (omit if separatory tube is used)	
4 Pipette droppers (medicine droppers)	
2 Pipette droppers (graduated at 0.5 and 1 ml)	
2 Porcelain perforated discs (beveled edge)	20 mm

Locker Equipment (Returnable) (*Continued*)	
6 Test tubes Pyrex 200 x 25 mm (8-inch)	
6 Test tubes Pyrex 200 x 25 mm with side arm	
6 Test tubes 150 x 20 mm (6-inch)	
6 Test tubes 100 x 12 mm (4-inch)	
6 Test tubes 75 x 10 (3-inch)	
1 Thermometer (preferably standardized for 76 mm immersion) 300° or 360°	
1 Stopcock for test-tube micro-desiccator	
1 Watch glass	50 mm
1 Watch glass	75 mm

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1 Bath for heating (Sm)
1 Burner (micro)
2 Clamps (Hoffman, screw)
4 Clamps (Burette)
1 Cork-borers set 1–6 or 1–8
1 Spatula monel blade Sm
1 Test-tube rack, Organic Sm

[1] This list is intended primarily for colleges and universities that offer instruction in qualitative organic analysis. It should be emphasized that many of the operations can be successfully performed with less specialized equipment. From this list, however, instructors and workers in industrial laboratories can select the apparatus required. Sources for semimicro apparatus appear in footnotes of pages in chapters 2, 3, and 8, where their use is described.

LOCKER EQUIPMENT (RETURNABLE) (*Continued*)

1 Test-tube holder
8 ft Rubber tubing 5 mm
1 ft Rubber tubing 3 mm
3 ft Burner tubing (rubber)
2 ft Rubber tubing for suction
12 Reagent bottles, Sm., 1 oz. capacity; square of flint glass with black screw-cap holding dropper (For acids, bases, water, methanol and ethanol).
6-8 Reagent bottles ½ oz. same as above (For benzene, ether, and other solvents)
12 Bottles for solids ½ oz. capacity with screw cap (For storing of derivatives)

NONRETURNABLE EQUIPMENT

12 Paper drying discs or Porous microplates	
50 Filter paper circles	22 mm
25 Filter paper circles	10–12 cm
1 File, rat tail	100 mm
1 File triangular	100 mm
1 Wire gauze	125 mm
1 Test-tube brush	32 mm
1 Test-tube brush	15 mm
25 Labels for reagent bottles	
6 ft. Glass tubing, soft	8 mm
6 ft. Glass tubing, soft	6 mm
6 ft. Glass tubing, soft	4 mm
1 ft. Glass rod, soft	6 mm
2 ft. Glass rod, soft	4 mm
2 Boxes of matches	
1 Towel	

PERMANENT EQUIPMENT FOR LOAN OR SIDE BENCH

Balances (horn pan; triple beam; Salvioni-Alber; semiquantitative)
Ceramic ink
Corks
Condenser for microfractionation
Disperser for microhydrogenation
Drying apparatus (Pyrex or Benzamin)
Fractionating column Sm
Fractionating column and jacket (Podbielniak)
Fractionating tube (Emich)
Fractionation apparatus under reduced pressure
Glass wool (crinkle, for packing of column)
Filter stick
Melting point apparatus (modified Thiele; Koefler; Dennis; Hershberg; Metal block)
Melting point flask (for m.p. between −50° to +40°)
Manometer
Microsublimation apparatus
Polarimeter
Paper for cleaning slides (facial tissue)
Pycnometers 1 ml and 2 ml
Specific Gravity pipettes (Alber A and B)
Refractometer (with liquids for reference of refractive indices)
Ring stands and rings
Rubber stoppers
Slides (microscope, with and without depression)
Suction pump
Tirrel burner with wing top
Tripods
Weights (50 mg − 5 g)

II. List of Reagents and Chemicals

It is assumed that all laboratories are supplied with concentrated hydrochloric acid, nitric acid, sulfuric acid and ammonium hydroxide and with the usual 6 *N* dilutions of these chemicals and sodium hydroxide, hence, they are not included in the listings. In many instances the same chemical is used in several different per cent concentrations in different parts of the text and where this is the case only the most concentrated solution is listed; for example, sodium hydroxide in aqueous solution is used as 6 *N*, 10 per cent, 5 per cent, and 2.5 per cent solutions but it is expected that the lower concentrations will be prepared as needed by diluting the 10 per cent stock solution. All of the chemicals that are recommended for any use in the text have been listed. A large percentage of the experiments can be made with a much less extensive list of chemicals since many of the listed chemicals are for single tests or are for the preparation of derivatives in cases where several different reagents can be effectively used.

Special Reagents

Barfoed's reagent. Dissolve 16.6 g of crystallized copper acetate in 245 ml of water and add 2.4 ml of glacial acetic acid.

Benedict's reagent. Dissolve 4.3 g of finely pulverized copper sulfate in 25 ml of hot water; cool and dilute to 40 ml with water. Dissolve separately 43 g of sodium citrate and 25 g of anhydrous sodium carbonate (or an equivalent amount of the hydrate form) in 150 ml of water. Heat to effect solution; cool; then add the copper sulfate solution and dilute to 250 ml. Keep the solution in a cork-stoppered bottle.

Ceric nitrate reagent. Dissolve 90 g of ceric ammonium nitrate, $Ce(NH_4)_2(NO_3)_6$, in 225 ml of warm 2 *N* nitric acid.

"Doctor" solution (sodium plumbite reagent). Dissolve 45 g of sodium hydroxide in 240 ml of water and then dissolve 7.5 g of litharge (PbO) in the hot caustic solution.

Fehling's reagent. This reagent is made at the time it is to be used by mixing equal volumes of the "A" and "B" solutions prepared as follows:

A. Dissolve 17.3 g of crystallized copper sulfate in enough water to make 250 ml of solution.

B. Dissolve 35 g of sodium hydroxide and 90 g of crystallized sodium potassium tartrate (Rochelle salt) in enough water to make 250 ml of solution.

Indicators: (1) *Universal, or long-range, indicators.* Several long-range indicators are commercially available. The one developed by one of the authors is prepared by the Synthetical Laboratories, Chicago, Illinois, and is sold under the trade name of *Sylco Universal Indicator* through laboratory supply dealers. Price: $5.00 per liter; color charts 40 cents each. The color chart has fifteen colors corresponding to *p*H 1–13. The *Gramery Universal Indicator* is prepared by Fisher Scientific Company, Pittsburgh, Pennsylvania, and Eimer and Amend, New York City. Price: $8.00 per liter, with one color chart included. The chart has twelve colors corresponding to *p*H 4–10. The *Harleco Universal Indicator* is prepared by the Hartman-Ledon Company, Philadelphia, Pennsylvania. Price: $9.00 per liter; color charts: 25 cents each. The color chart has one blended color scale corresponding to *p*H 1–13.

(2) *Sulfonphthalein indicators.* Place 0.4 g of the sulfonphthalein indicator in a 250 ml flask and add 12 ml of 0.1 *N* sodium hydroxide solution and 50 ml of water. Warm until the dye is completely dissolved. Dilute to 200 ml and filter into a bottle. Add 100 ml of water through the filter to wash the adhering dye, and then make up

the solution to a volume of one liter by adding 700 ml of water. Since excess of alkali was used to effect solution, standardize the indicator solution as follows: Add one drop at a time of 0.1 *N* acid and shake; compare the color of the foam with the color chart of sulfonphthalein indicators which appears in W. M. Clark's *The Determination of Hydrogen Ions.* (A separate color chart can be obtained from Williams and Wilkins, Baltimore, Maryland; price: $1.00.) When the color of the foam corresponds to the color of the midpoint indicated in the chart by an arrow, the indicator is ready for use. If the midpoint is passed, add dropwise 0.1 *N* solution of sodium hydroxide. It is preferable to store the indicator solution in Pyrex bottles (rubber-stoppered). Storage in soft glass changes the *p*H. The standardization described is accurate for most purposes where indicator solutions are used by students. If greater accuracy is required, the solution may be standardized by a glass or quinhydrone electrode.

(3) *Additional indicators.* Most indicator solutions for general use can be prepared by dissolving 50-100 mg of the indicator in 100 ml of 90 per cent methanol.

Lucas reagent. Dissolve 320 g of anhydrous zinc chloride in 200 ml of concentrated hydrochloric acid.

Millon's reagent. Dissolve 100 g of mercury in 75 ml of concentrated nitric acid (do not heat externally); dilute the solution with 135 ml of water and stir concentrated nitric acid into the mixture as may be necessary to dissolve any precipitate.

Molisch's reagent. Dissolve 2.5 g of pure α-naphthol in 25 ml of ethanol or methanol. This reagent should have been made within a few days of the time it is used.

Molybdic acid reagent. Dissolve 75–100 mg of molybdic acid in 10 ml of concentrated sulfuric acid by heating and stirring the mixture. Prepare this reagent at the time it is to be used.

Schiff's fuchsin aldehyde reagent. Dissolve 250 mg of *p*-rosaniline hydrochloride (fuchsin) in 50 ml of warm water. Cool and saturate the solution with sulfur dioxide until the pink color has disappeared. Add 250 mg of decolorizing carbon, shake, filter and dilute to 250 ml. If the stock solution develops a pink color, repeat the saturation with sulfur dioxide before using it.

Seliwanoff's reagent. Dissolve 125 mg of pure resorcinol in 250 ml of dilute hydrochloric acid (83 ml of concentrated acid and 167 ml of water).

Tollen's reagent. This reagent is unstable and should be made at the time it is to be used by following the directions given in experiment 6.37-c (page 147).

General Reagents

All solutions are aqueous unless some other solvent is specified. In cases where the salt is usually obtained in the hydrated form the actual weights of chemicals are given to make the desired concentration of the anhydrous compound. It is assumed that the less concentrated per cent solutions will be made as needed from the stock solutions listed here.

Acetaldehyde, 5 per cent.
Ammonium molybdate, 5 per cent.
Barium chloride, 5 per cent.
Benzidine, 5 per cent in glacial acetic acid.
Sodium bisulfide (or potassium bisulfide), 10 per cent. (This reagent may be prepared by bubbling hydrogen sulfide into a 10 per cent solution of sodium or potassium hydroxide until the *p*H reaches about 8.)
Bromine, 2 per cent in carbon tetrachloride; also 2 per cent in glacial acetic acid.

Chloranil (tetrachloroquinone), a saturated solution in dioxane.
Ferric chloride, 10 per cent (16 g of the hexahydrate per 100 ml of solution).
Formaldehyde, 40 per cent (formalin).
Hydrochloric acid, 10 per cent
Hydrogen peroxide, 3 per cent.
Hydroxylamine hydrochloride, 1 *N* in methanol (7 g in 100 ml).
Iodine, saturated solution in water; also, 0.5 per cent in carbon disulfide; also, 10 per cent iodine in a 20 per cent solution of potassium iodide.
Isatin, 1 per cent in concentrated sulfuric acid.
Lead acetate, 5 per cent; also, a saturated solution in ethanol.
Methone (dimethyldihydroresorcinol), 5 per cent in ethanol.
Nickelous chloride, 10 per cent.
Phenol, 4 per cent.
Potassium dichromate, 5 per cent.
Potassium hydroxide, 5 *N* in 80 per cent methanol (28 g dissolved in 20 ml of water, then diluted to 100 ml with methanol); also, 2 *N* in 80 per cent methanol (10 ml of the 5 *N* diluted to 25 ml with 80 per cent methanol); also, 6 *N* in water (33.6 g in 100 ml).
Potassium periodate, 5 per cent.
Potassium permanganate, 1 per cent.
Silver nitrate, 5 per cent; also, a saturated solution in ethanol.
Sodium acetate, 10 per cent (16.5 g of the trihydrate per 100 ml of solution).
Sodium bicarbonate, 10 per cent.
Sodium carbonate, 10 per cent.
Sodium hydroxide, 10 per cent; also, 6 *N* (24 g per 100 ml of solution).
Sodium hypochlorite, 5 per cent ("Chlorox").
Sodium nitroprusside, 1 per cent.

Pure Chemicals

Acetic acid, glacial
Acetic anhydride
Acetyl chloride
Aluminum chloride
Aluminum ethoxide
Aniline
Barium hydroxide
Benzene
Benzenehydroxamic acid
Benzenesulfonyl chloride
Benzidine
Benzoyl chloride
Benzylamine
Benzyl chloride
S-benzylthiuronium chloride
Bromine
p-Bromoaniline
p-Bromobenzenesulfonyl chloride
p-Bromophenacyl bromide
Butanol
Calcium chloride
Carbon disulfide
Carbon tetrachloride
Charcoal (also decolorizing carbon)
Chloroacetic acid
Chloroplatinic acid
Chloroform
Chlorosulfonic acid
Copper sulfate (hydrated and anhydrous)
4,4′-Diaminodiphenylmethane
Diethylene glycol
Dimethylaniline
3,5-Dinitrobenzoic acid
3,5-Dinitrobenzoyl chloride
2,4-Dinitrochlorobenzene
2,4-Dinitrophenylhydrazine

Dioxane
Diphenylanmine
Ethyl acetate
Ethanol
Ethyl ether
Ferrous ammonium sulfate
Ferrous sulfate
Glycerol
Hydrazine sulfate
p-Hydroxybenzoic acid
Hydroxylamine hydrochloride
Isopropyl alcohol
Ligroin
Magnesium
Mercuric iodide
Mercuric oxide
Mercuric sulfate
Methone (dimethyldihydroresorcinol)
Methanol
Methyl iodide
Methyl-*p*-toluenesulfonate
α-Naphthol
α-Naphthyl isocyanate
Nitric acid, fuming
m-Nitrobenzenesulfonyl chloride
p-Nitrobenzoyl chloride
p-Nitrobenzyl chloride
Nitrosyl chloride
p-Nitrophenylcarbamyl chloride
p-Nitrophenylhydrazine
p-Nitrophenylhydrazine hydrochloride
3-Nitrophthalic anhydride
Phenacyl chloride
Phenol
Phenolphthalein
o-Phenylenediamine
Phenylhydrazine
Phenylhydrazine hydrochloride
2-Phenylindole
Phenyl isocyanate
Phenyl isothiocyanate
Phloroglucinol
Phosphoric acid, 85 per cent
Phosphorous pentachloride
Phosphorous pentoxide
Phthalic anhydride
Picric acid
Potassium carbonate, anhydrous
Potassium dichromate
Potassium hydroxide
Potassium iodate
Potassium phthalimide
Potassium thiocyanate
Pyridine
Semicarbazide
Semicarbazide hydrochloride
Silver 3,5-dinitrobenzoate
Sodium
Sodium acetate
Sodium anthraquinone *α*-sulfonate
Sodium bisulfite
Sodium carbonate, anhydrous
Sodium hydroxide
Soda-lime
Sodium nitrite
[illegible] sulfate, anhydrous
S[illegible]m saccharin
Stannous chloride
Sulfur
Thioglycollic acid
Thionyl chloride
Thiourea
Tin
Toluene
p-Toluenesulfonyl chloride
o-Toluidine
p-Toluidine
p-Tolyl isocyanante
Triiodophenol
Xanthydrol
Zinc, dust
Zinc chloride, anhydrous

III. Laboratory Accidents and First Aid

In case of *fire* or *accident* call the laboratory instructor *at once* if possible. But there are times when seconds count, and the student should be ready in such cases to administer first aid to himself and others and to put out a fire before it spreads.

Fire from burning reagents. If the liquid in a beaker or flask catches fire, the source of heat should be removed and the flame extinguished by placing a watch-glass or a damp cloth over the opening of the vessel. If the vessel is large, use an asbestos blanket and, if necessary, a fire extinguisher—but not water. If a carbon-dioxide fire extinguisher is available, use it by directing the discharge nozzle first toward the edge of the fire and then toward the middle. If a carbon tetrachloride fire extinguisher is used, **ventilate the room at once,** as vapors of this substance are toxic.

For burning oil, if carbon dioxide is not available, use a mixture of sand and sodium bicarbonate, or of sand and ammonium chloride. **Do not use water,** as it will only spread the fire.

Burning clothing. If the clothing should catch fire, remove it if possible, or avoid running, as this will fan the flame. Smother the flame by wrapping the body in a laboratory coat or, preferably, in a woolen blanket kept under the first-aid cabinet for that purpose.

Burns. The basis for the treatment of all burns is to maintain sterility and to promote granulation and the formation of new tissues. In the case of burns from chemicals, the first important aid is **immediate washing with water,** followed by washing with a very dilute solution of another substance that will neutralize the chemical which caused the injury. Following are specific treatments.

(*a*) *Burns from fire.* For slight burns in which the skin is not broken, apply one of the following ointments: *Unguentine, Butesin Picrate, Tannic Acid Jelly,* or *Crystal Violet Jelly.* The ointment is applied to the skin and, if necessary, the part is bandaged. The use of cotton is to be avoided. If the pain is severe, a compress moistened with a 3 per cent solution of aluminum acetate, $Al_2O(C_2H_3O_2)_2 \cdot 4\ H_2O$, may be applied and left until the pain is relieved. Then the skin should be dried, and either ointment or antiseptic talcum powder should be applied.

When the burn is large and severe, call a physician at once. If emergency treatment is required and a physician is not available within fifteen minutes, place the patient on a cot and cover him with blankets, but be careful to avoid touching the burned parts. Remove adhering clothing from the burned parts and cover with one of the jellies mentioned above, pending the physician's arrival. In order to relieve the severe pain, apply compresses with aluminum acetate or a gauze moistened with 1 to 2 per cent aqueous solution of a local anesthetic.

(*b*) *Chemicals in the eye.* Wash the eye immediately with a large amount of water. If the chemical is an acid, flushing with water should be followed by application of a 1 per cent solution of sodium bicarbonate. An eye cup is very convenient for this purpose. If the chemical is an alkali, flushing with water should be followed by application of a 1 per cent solution of boric acid. After washing with water and dilute neutralizing solution, a drop of sterile olive oil[1] should be applied and the patient should be taken to a physician. Injuries to the eye require a specialist's care.

[1] The authors use olive oil that contains 1–2 g of ethyl *p*-aminobenzoate per 100 ml and that has been heated to 110° for a few minutes. For the same purpose an ophthalmic ointment containing 2 per cent butyn sulfate may be used.

(*c*) *Acids and alkalies on the skin.* Wash with large amounts of water. In the case of acids, follow by application of a paste of sodium bicarbonate and allow to remain for 15–20 minutes. Then remove the excess, dry, and cover the skin with an ointment. In the case of alkalies, after washing with water, rinse the affected parts with a saturated boric acid solution or a 1 per cent solution of acetic acid. Then dry the skin and cover with tannic acid jelly.

(*d*) *Bromine burns.* Wash at once with water and a 2 per cent solution of sodium thiosulfate. Cover immediately with glycerin and follow with an ointment.

(*e*) *Organic substances.* Rinse at once with water and remove any insoluble part by washing with ethyl alcohol. This may be followed by washing with soap and water. Dry the skin and apply an ointment.

Cuts. If the cut is a minor one, allow it to bleed for a few seconds, wash it with water, and then apply a prepared bandage with an antiseptic center. If a ready-made bandage is not available, apply an antiseptic from the first-aid cabinet and then cover the wound with a sterile 1- or 2-inch bandage. In case of profuse bleeding, wash the cut and apply a bandage, using pressure about four inches above and below the cut to diminish circulation and to aid clotting. Continuous pressure should not be maintained for more than five minutes. When a clot has formed, apply a mild antiseptic and call a physician.

IV. Preparation of Pipettes and Pipette Droppers

For semimicro work a number of small pipettes and pipette droppers are used. Pipette droppers having a glass tube 80–90 mm in length and 6 mm in diameter (1–2 mm at the point) are commercially available. Pipettes and pipette droppers of greater length and smaller capillary diameter are prepared as needed.

Pipettes for semimicro separation of immiscible liquids. In conjunction with the use of the separatory tube for separating two immiscible liquids, a pipette with a long capillary thread is very useful for removing the last few drops. In the separation of organic liquids from water or in the extraction of aqueous liquids from ether it is extremely difficult to remove every drop of water. Droplets of water adhere to the sides of the tube or separatory funnel, or remain suspended in the organic liquid, and on standing accumulate and form a thin layer. This can be removed with a pipette having a capillary thread 60–80 mm in length and 0.05–08 mm in diameter at the end of the capillary. A rubber bulb fitted to the wide end of the tube completes the capillary pipette.

To prepare a pipette, clean thoroughly with soap and water a piece of soft glass tubing 200 mm in length and 6–8 mm in diameter. Rinse well first with tap water and then with distilled water. Allow it to dry. Use either a good Bunsen flame or, if not familiar with elementary manipulations, use a burner provided with a wing top. Grasp the ends of the glass tubing with both hands and rotate it between the thumb and index finger over the flame. When the glass has softened enough to bend easily, remove from the flame and draw gently and steadily lengthwise until the length has doubled. Hold in place until the glass has hardened and then lay it carefully on an asbestos mat. The capillary is then cut in about the middle. The wide end of the pipette is heated until it is fire polished. If the glass tubing used is of 6-mm bore, the wide end is flanged in order to form a tight fit with the rubber bulb. To flange the end, heat it in the flame until the tube has softened; then press firmly against an asbestos pad. The operation is repeated until a flange 7–8 mm in diameter is formed.

Pipette droppers. Pipette droppers of various sizes are made by a method similar to that described for the capillary pipette. A piece of glass tubing 160 mm in length and 6 mm in diameter is heated over the flame and then pulled very slowly until the length of the tube has increased to 180–190 mm. The tube is held in place until cold and then the drawn part is cut into two equal lengths. The capillary end is heated carefully in the flame to smooth the glass, and the wide end is flanged as before. It is suggested that several of these droppers be made since the rubber bulb may be changed from one dropper to another.

V. Cleaning Solutions

Chromic acid cleaning mixture. Dissolve 10 g of sodium dichromate in 10 ml of water in a 400 ml beaker. Add slowly with careful stirring 200 ml of concentrated sulfuric acid. The temperature will rise to nearly 80°C. Allow the mixture to cool to about 40°C. and place in a dry glass-stoppered bottle. Care should be exercised in making and handling this solution.

Trisodium phosphate solution. Glassware that does not contain tars may be cleaned with a 15 per cent solution of trisodium phosphate. A warm solution with the aid of an abrasive powder, such as pumice, is safer to handle and cleans as well as or better than chromic acid solutions.

VI. Drying Agents for Organic Liquids

Drying agents are used to remove small amounts of water from organic compounds. The desirable features which are to be considered in selecting a drying agent are: (1) it should not react or combine with the compound to be dried; (2) it should not catalyze polymerizations or condensation reactions; (3) it should have a high drying power; (4) it should be economical (if the initial cost is high, it should be possible to regenerate it by dehydration).

Common Drying Agents for Organic Compounds

Anhydrous substance	*Applicable to*	*Not applicable to*	*Drying power*	*Relative efficiency*
Calcium chloride	Hydrocarbons, halides, ethers, esters	Hydroxy and amino compounds	High below 30°	Medium
Calcium sulfate ("Drierite")	All compounds	None	Low	Good
Magnesium sulfate	All compounds	None	High	Good
Potassium carbonate	Amines, alcohols, ketones	Acids	Medium	Medium
Potassium hydroxide	Amines, hydrazines, saturated hydrocarbons	Most compounds	High	Good
Phosphorus pentoxide	Halides, hydrocarbons, nitriles	Most compounds	High	Excellent
Sodium hydroxide	Amines, hydrazines, saturated hydrocarbons	Most compounds	High	Excellent
Sodium metal	Ethers, saturated hydrocarbons	Most compounds	High	Excellent

VII. The Neutralization Equivalent

The neutralization equivalent of an acid or acidic compound is actually its equivalent weight and hence it is of value in identifying the compound. In case the substance is a liquid it is best to weigh it in a dropping-bottle and then transfer a few drops of the liquid to the titration flask and re-weigh the dropping-bottle. The weight of the sample is the difference in the two weights of the dropping-bottle. If the substance is even reasonably volatile, it is best to have the solvent (water, alcohol, or a mixture of water and alcohol depending on the solubility of the substance) in the titration flask before adding the substance so as to retard its evaporation.

Transfer an accurately weighed sample (100–300 mg) of the acidic substance to a 125–250 ml flask and add 25–35 ml of water, alcohol, or a mixture of these solvents to dissolve the substance. Titrate the solution with a standardized solution of sodium hydroxide (approximately 0.1 *N*), using phenolphthalein as the indicator. Calculate the neutralization equivalent of the compound as follows:

$$\text{N.E.} = \frac{\text{Wt. of sample in grams} \times 1000}{\text{ml of NaOH} \times N \text{ of the NaOH}}$$

This formula may be written as:

$$\text{N.E.} = \frac{\text{Milligrams of sample}}{\text{Milliequivalents of NaOH}}$$

VIII. The Saponification Equivalent of an Ester

Several methods are in common use for the determination of the saponification equivalent of an ester. The objective is to hydrolyze the ester and determine the amount of alkali that reacts with the acid produced. Saponification of an ester by aqueous sodium hydroxide is inhibited by the fact that most esters are sparingly soluble in the aqueous solution. Solutions of potassium hydroxide in diethylene glycol have been used.[1] It has been found that a solution of potassium hydroxide in methanol, ethanol, propanol, or 2-propanol makes a satisfactory saponifying agent. The alcoholic solution of potassium hydroxide tends to attack glass and to absorb carbon dioxide from the air during the refluxing of the mixture, hence it is wise to standardize the alkaline solution under conditions which are similar to those used for the saponification of the ester. Since many esters are at least moderately volatile it has been found advisable to have the alcoholic solution of potassium hydroxide in the flask before adding the weighed sample of the ester so as to dissolve the ester and decrease its loss by evaporation. Liquid esters should be *weighed by difference* from a dropping-bottle.

Dissolve approximately 3 g of potassium hydroxide in 60 ml of alcohol and allow any sediments to settle. Add exactly 25 ml of the alcoholic solution of potassium hydroxide to each of two 125–250 ml flasks. To one of the flasks, add an accurately weighed sample (300–400 mg) of the ester and use the other flask as a "blank." Attach reflux condensers to both flasks and gently boil the solution for one hour. Cool the solutions and rinse each condenser with 10 ml of water, catching the washings in the solutions. Titrate each of the solutions with standardized hydrochloric acid (approximately 0.5 *N*) using phenolphthalein as an indicator.

[1] Redemann and Lucas, *Ind. Eng. Chem., Anal. Ed.*, **9**, 521 (1937).

The difference in the volumes of hydrochloric acid required for the solution which contained the ester and that required for the "blank" represents the amount of potassium hydroxide which reacted with the ester. The number of milliliters of a solution multiplied by the normality of the solution equals the number of milliequivalents, hence the volume of the hydrochloric acid (the difference in the volumes required for the two titrations) multiplied by the normality of the hydrochloric acid equals the milliequivalents of potassium hydroxide required for the ester. Calculate the saponification equivalent of the ester as follows:

$$\textit{Saponification Equivalent} = \frac{\text{Milligrams of ester}}{\text{Milliequivalents of KOH}}$$

Saponification number. Industrially, the saponification number is more generally used than the saponification equivalent.[1] The saponification number is defined as the number of milligrams of potassium hydroxide required to saponify one gram of the oil or fat. It may be calculated from the data obtained from the determination of the saponification equivalent by the use of the following formula:

$$\textit{Saponification Number} = \frac{\text{Milliequivalents of KOH} \times 56.1}{\text{Grams of ester}}$$

IX. The Iodine Number of a Fat or Oil

The chemical literature records several fundamental methods and many modifications of those methods for the determination of the *iodine number* (centigrams of iodine absorbed per gram of the sample). Two procedures have been selected, one for a macro quantity, and one for a micro quantity. The iodine numbers, as determined by various methods, do not always agree.

Macro method

The method used here is that of Wijs. More details of this method and also other methods are given in the *Official and Tentative Methods of the American Oil Chemists Society* and the *Official and Tentative Methods of the Association of Official Agricultural Chemists*[2] publications.

Add 100–400 mg of the sample to a 250–500 ml glass-stoppered flask containing 20 ml of carbon tetrachloride (or chloroform). Add 25 ml of the iodine solution (Wijs) which has been prepared by dissolving 13 g of pure iodine in a liter of pure acetic acid and then passing chlorine gas into the solution until the quantity of sodium thiosulfate required for titration is not quite doubled.[3] Moisten the stopper with 5 drops of a 15 per cent solution of potassium iodide. Let the flask stand in the dark for 30 minutes and then add 20 ml of 15 per cent potassium iodide and 100 ml of water. Titrate the solution with sodium thiosulfate (about 0.1 N) until the yellow color almost disappears and then add 3 drops of a 1 per cent starch suspension and continue the titration until the blue color entirely disappears. Near the end of the

[1] For a direct method of determining the saponification number, see: *Official and Tentative Methods of Analysis*, 5th Ed. (1940), page 432; Association of Official Argicultural Chemists, P. O. Box 540, Benjamin Franklin Station, Washington, D. C.

[2] 5th Ed. (1940), pages 66, 95, 113, 115, 206, 429, 472. Published by the Association of Official Agricultural Chemists, P. O. Box 540, Benjamin Franklin Station, Washington, D. C.

[3] An alternative method uses dichloramine T as the source of the chlorine. See *Analyst* **58,** 523 (1933); cf. C. A. 27, 5562 (1933).

titration, shake the solution vigorously. Run a "blank" determination (without the fat or oil). The *iodine number* is the number of centigrams of iodine which reacts with one gram of fat or oil.[1]

$$\textit{Iodine Number} = [(V \times N \text{ of } Na_2S_2O_3 \text{ for "blank"}) - (V \times N \text{ of } Na_2S_2O_3 \text{ for sample})] \times 0.127 \times \frac{100}{\text{wt. of sample}}$$

Micro method

The Kaufman method[2] is given here because it is recommended in the literature[3] and because it has proven satisfactory in the laboratory of one of the authors. The reagents required are:

(a) 0.1 *N* bromine in methanol saturated with dry sodium bromide.
(b) 10 per cent potassium iodide.
(c) 0.05 *N* sodium thiosulfate.
(d) alcohol-free chloroform.

The fat or oil (10–30 mg) is dissolved in 2 ml of chloroform in a 150 ml iodine flask. Place 2 ml of chloroform in another flask and use it as a "blank" to be treated by the same procedures as the sample. Exactly 5 ml of the 0.1 *N* bromine solution are added from a micro burette. The mixture is shaken. The reaction is complete in 1–5 minutes. Add 3 ml of the potassium iodide solution and shake the mixture. The excess bromine reacts with the potassium iodide to liberate free iodine which is then titrated with the sodium thiosulfate solution. Since the number of milliequivalents of sodium thiosulfate is equal to the number of milliequivalents of excess bromine and since the milliequivalent weight of iodine may be considered as 0.127, the following equation may be used to calculate the iodine number:

$$\textit{Iodine Number} = [V \times N \text{ of } Na_2S_2O_3 \text{ for "blank"}) - (V \times N \text{ of } Na_2S_2O_3 \text{ for sample})] \times 0.127 \times \frac{100}{\text{wt. of sample}}$$

X. Precautions in handling sodium

The experienced worker needs no directions for the use of sodium, but it is considered advisable to remind the beginner that sodium must be kept under an inert liquid such as kerosene or toluene, and must be handled away from water. To prepare sodium cuttings, such as are used for the sodium fusion test (page 91), a piece of sodium metal is removed by means of rubber finger-stalls or handled with paper, and is cut rapidly into small pieces with a knife. The small pieces are put back into a dish or bottle as they are cut, so that they are kept covered with the inert solvent. When a piece of sodium is required it is placed between filter papers

[1] Scotti has modified the Wijs method to shorten the time required. See:
a. *Oil and Soap* **16**, 236 (1939); c.f. C. A. **34**, 901 (1940).
b. *Olii minerali, grassi e saponi, colori e vernici*, **18**, 96 (1938); c.f. C. A. **34**, 429 (1940).

[2] *Ber.* **70 B**, 2554 (1937); c.f. C. A. **32**, 1961 (1938).

[3] a. *Fette u. Seifen* **43**, 155 (1936); c.f. C. A. **31**, 2034 (1937).
b. *Biochem Z.* **296**, 174 and 180 (1938); c.f. C. A. **33**, 420 (1939).
c. *Oil and Soap* **16**, 69 (1939); c.f. C. A. **33**, 4446 (1939).
d. *Fette u. Seifen* **47**, 4 (1940); c.f. C. A. **34**, 4291 (1940).
e. *Wollen- u. Leinen- Ind.* **60**, 67 (1940); c.f. C. A. **34**, 7635 (1940).
f. *Inst. espafi. oceanograf. Notas y resúmenes. Ser.* **2**, No. 111, 5 (1942); c.f. C. A. **37**, 5263, (1943).

and pressed so as to remove the solvent and then used as directed. All the papers and vessels that have been used in handling sodium are carefully examined for adhering pieces, then are placed in the hood and washed with methanol before disposal Goggles should be worn throughout all experiments in which sodium is used.

Indexes

Index of Text

Index of Tables

All compounds listed in the left-hand column of each table under the head "Name of Compound" are included in this index; any compounds not listed may be found in the columns of derivatives following the names of the appropriate parent compounds.

Compounds are listed alphabetically under their own names rather than by chemical classes.

The page references follow immediately after the name of each compound. The number assigned each compound in the left-hand column of the table in which it appears is given in parentheses after the page reference; any compound listed without a number enclosed in parentheses following the page reference is to be found in Table 42.